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In this issue:

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on the Liability to Psychiatric Illness
By Kenneth S. Kendler

Drugs and the DST: Need for a Reappraisal
By Robert P. Kraus, Paul Grof, and Gregory M. Brown

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By Barbara P. Illowsky and Darrell G. Kirch

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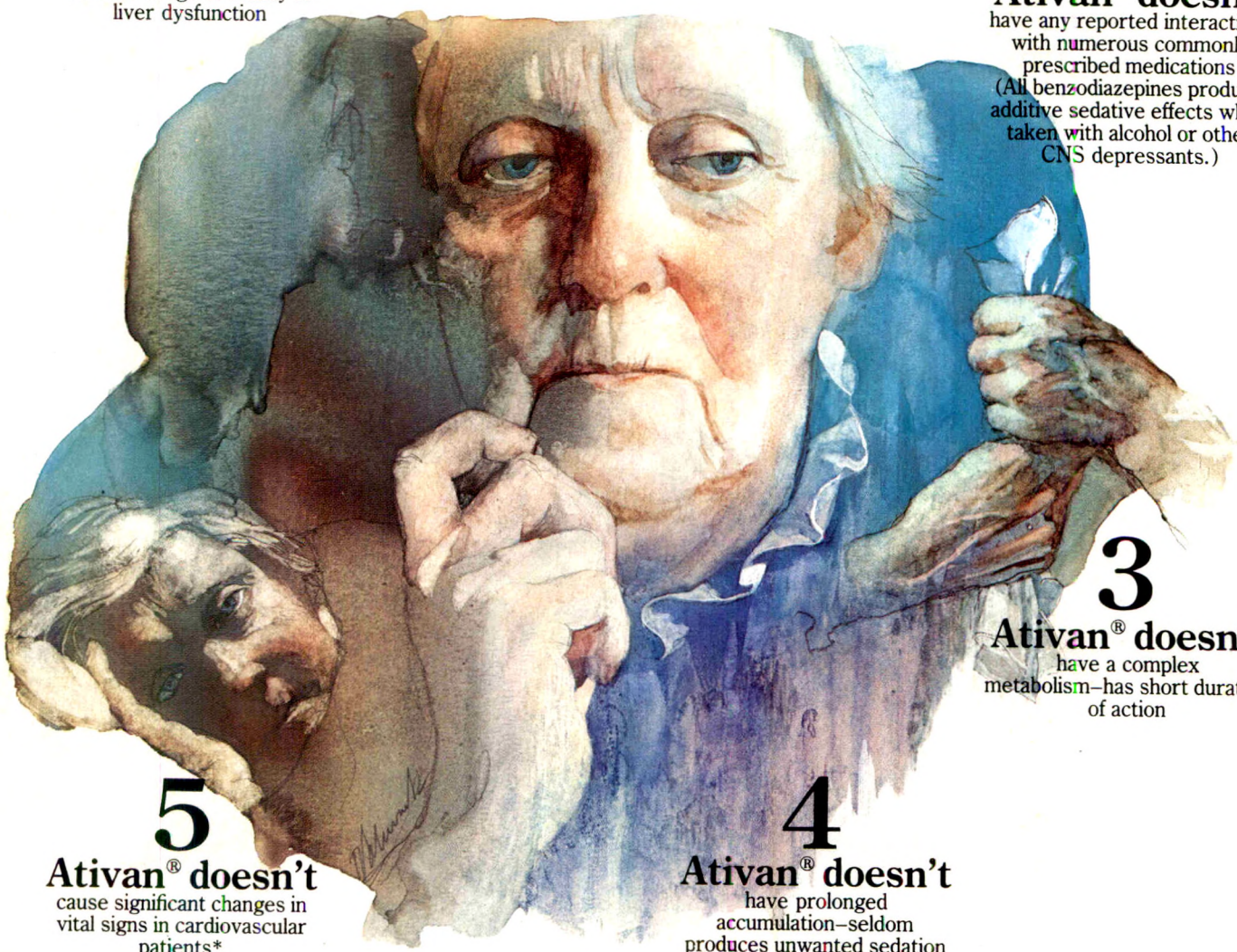
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no significant changes in vital signs in cardiovascular patients*

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e: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients *not to operate machinery or* motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia, some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.



DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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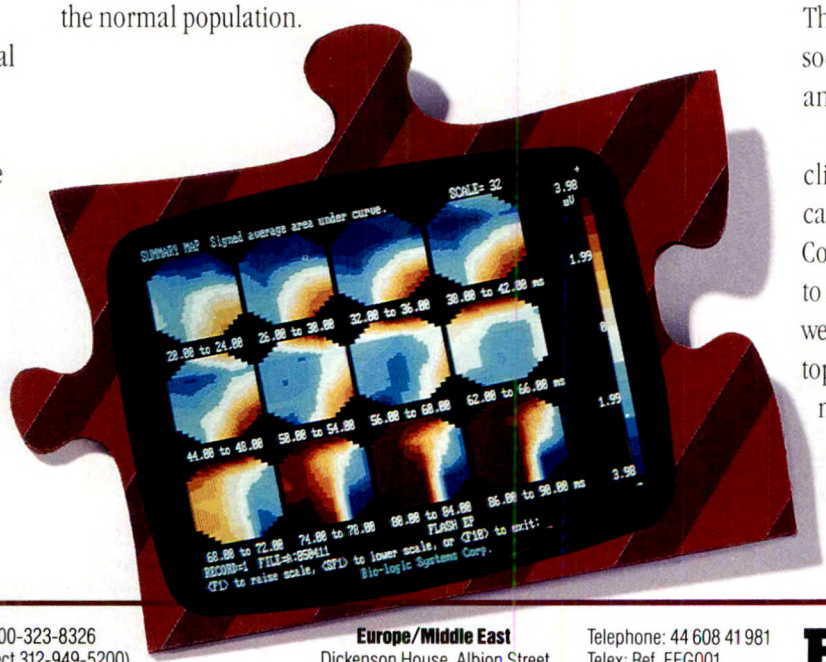
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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 145, Number 6 June 1988

SPECIAL ARTICLES

657 Indirect Vertical Cultural Transmission: A Model for Nongenetic Parental Influences on the Liability to Psychiatric Illness *Kenneth S. Kendler*

666 Drugs and the DST: Need for a Reappraisal *Robert P. Kraus, Paul Grof, and Gregory M. Brown*

675 Polydipsia and Hyponatremia in Psychiatric Patients *Barbara P. Illowsky and Darrell G. Kirch*

REGULAR ARTICLES

684 Gender Differences in the Course of Schizophrenia *Jill M. Goldstein*

690 Psychiatric Residents' Sexual Contact With Educators and Patients: Results of a National Survey *Nanette Gartrell, Judith Herman, Silvia Olarte, Russell Localio, and Michael Feldstein*

695 Refining the Diagnosis of Schizophreniform Disorder *Morton Beiser, Jonathan A.E. Fleming, William G. Iacono, and Tsung-yi Lin*

701 Effects of ECT on Brain Structure: A Pilot Prospective Magnetic Resonance Imaging Study *C. Edward Coffey, Gary S. Figiel, William T. Djang, Daniel C. Sullivan, Robert J. Herfkens, and Richard D. Weiner*

707 The Dexamethasone Suppression Index: Enhancement of DST Diagnostic Utility for Depression by Expressing Serum Cortisol as a Function of Serum Dexamethasone *George W. Arana, Seymour Reichlin, Robert Workman, Richard Haaser, and Richard I. Shader*

712 Psychiatric Disorder and Limitations in Physical Functioning in a Sample of the Los Angeles General Population *Kenneth B. Wells, Jacqueline M. Golding, and M. Audrey Burnam*

718 Some Differences Between Men and Women Who Commit Suicide *Charles L. Rich, Joanne E. Ricketts, Richard C. Fowler, and Deborah Young*

COMMENTARY

723 How to Survive in the Private Practice of Psychiatry *Steven S. Sharfstein and Allan Beigel*

BRIEF COMMUNICATIONS

728 Effects of Diagnosis and Context on Dangerousness *Renée L. Binder and Dale E. McNiel*

733 Epinephrine Infusions in Patients With Social Phobia *Laszlo A. Papp, Jack M. Gorman, Michael R. Liebowitz, Abby J. Fyer, Barry Cohen, and Donald F. Klein*

CLINICAL AND RESEARCH REPORTS

737 Suicide Attempts in Patients With Borderline Personality Disorder *Minna R. Fyer, Allen J. Frances, Timothy Sullivan, Stephen W. Hurt, and John Clarkin*

740 Prolactin Response to Tryptophan During Mianserin Treatment
Philip J. Cowen

742 Adjunctive Alprazolam for Schizophrenia With Panic Anxiety: Clinical Observation and Pathogenetic Implications *Jeffrey P. Kahn, Marilu A. Puertollano, Murray D. Schane, and Donald F. Klein*

745 Thyroid Indices in Panic Disorder *Murray B. Stein and Thomas W. Uhde*

748 A Carbamazepine Trial in Chronic, Treatment-Refractory Schizophrenia
John Sramek, John Herrera, Jerome Costa, Chris Heh, Tram Tran-Johnson, and George Simpson

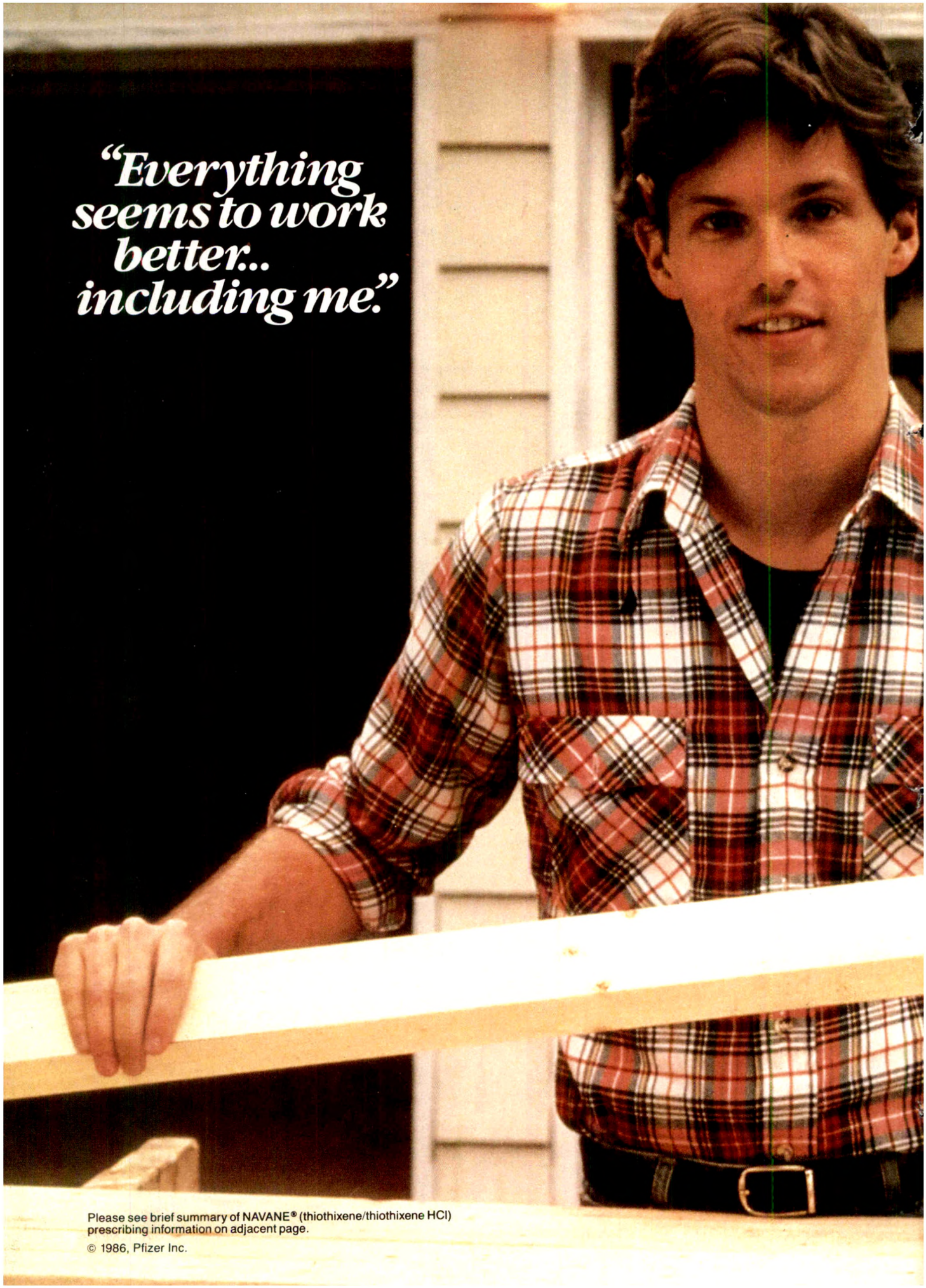
751 Videotape Recording of Inpatient Assaults: A Pilot Study
David A. Brizer, Martha L. Crowner, Antonio Convit, and Jan Volavka

753 Bulimia in College Women: Incidence and Recovery Rates
Adam Drewnowski, Doris K. Yee, and Dean D. Krahn

BOOK FORUM 756

LETTERS TO THE EDITOR 764

OTHER
A17 Officers of the American Psychiatric Association
A20 Calendar
A34 Index to Advertisers
A38 *Psychological Medicine* Contents
A39 Information for Contributors



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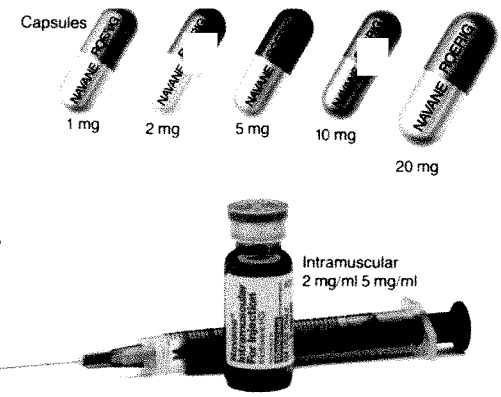
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Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
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Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

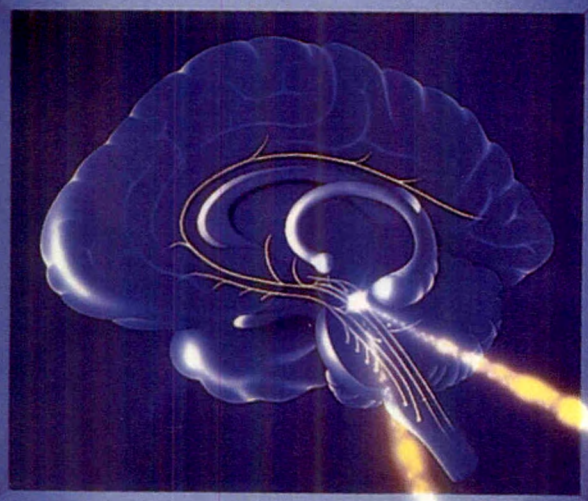
NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

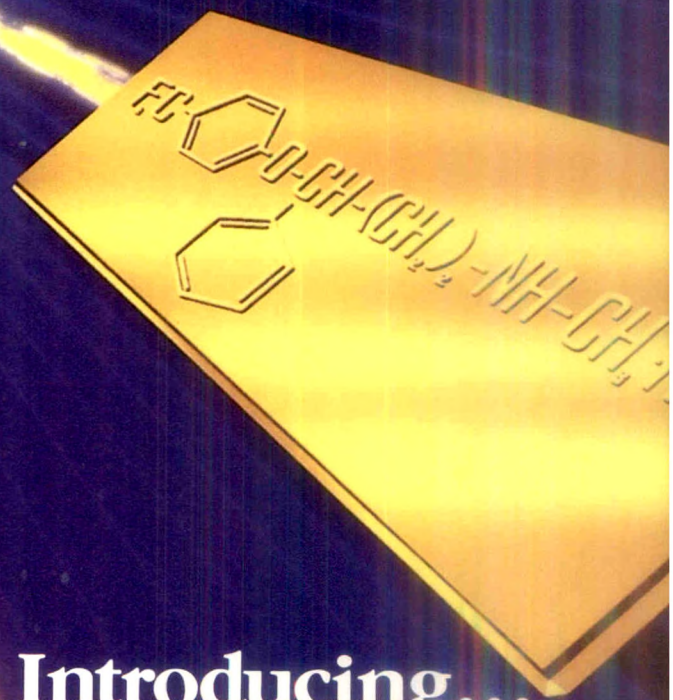
ROERIG Pfizer

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"There is considerable evidence that serotonergic function may be reduced in the brains of depressed patients."

Arch Gen Psychiatry 1984;41:398-402.



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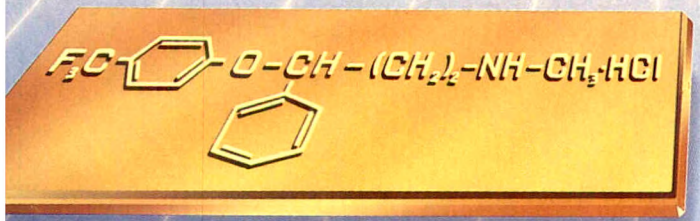
New

PROZAC®

fluoxetine hydrochloride

A *specifically* different antidepressant

Chemically unrelated to all other available antidepressants.



Its distinctive chemistry means greater specificity.

The first highly specific...highly potent blocker of serotonin uptake

Effective treatment for depression

Fewer side effects to disrupt therapy

Side effects with Prozac® (fluoxetine hydrochloride) are generally mild and manageable and include nausea, anxiety/nervousness, insomnia, and drowsiness

Rash and/or urticaria occurred in 4% of clinical trial patients

Wide margin of safety

20-mg once-a-day therapy

Please see following page for brief summary of prescribing information.

DISTA

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Please send me complete product information on Prozac® (fluoxetine hydrochloride)

NAME _____ MD

ADDRESS _____

CITY _____

STATE _____ ZIP CODE

Return to: Dista Products Company
P.O. Box 5321
FDR Station
New York, NY 10150

Prozac®
fluoxetine hydrochloride

Brief Summary. Consult the package insert for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindications: None known.

Warnings: *Rash and Accompanying Events*—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General*—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of Prozac-treated patients compared to 4% of placebo and 3% of tricyclic-antidepressant-treated patients. However, only rarely have Prozac patients been discontinued for weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Life of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. (*See* Clinical Pharmacology and Dosage and Administration sections).

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 753 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

- Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.
- Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.
- Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breast feeding an infant.
- Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monamine Oxidase Inhibitors—Although no clinical data are available on the effects of the combined use of fluoxetine and MAO inhibitors, it seems prudent to avoid their combined use until their potential for interaction has been studied systematically in controlled clinical trials. Based on experience with the combined administration of MAOI and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Prozac.

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients.

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children—Safety and effectiveness in children have not been studied.

Use in the Elderly—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Adverse Reactions: *Commonly Observed*—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials—The table that follows enumerates adverse events that occurred at a frequency of 1% or more among Prozac patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE
INCIDENCE IN PLACEBO-CONTROLLED
CLINICAL TRIALS

Body System: Adverse Event*	Percentage of Patients Reporting Event: Prozac (N = 1,730)	Placebo (N = 799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	—
Light-headedness	1.6	—
Concentration decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	—
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	—
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	—
Frequent micturition	1.6	—
Urinary tract infection	1.2	—
Special Senses		
Vision disturbance	2.8	1.8

*Events reported by at least 1% of Prozac patients are included
—Incidence less than 1%

Other Events Observed During the Premarketing Evaluation of Proza
During clinical testing in the US, multiple doses of Prozac were adm
tered to approximately 5,600 subjects. Untoward events associated
this exposure were recorded by clinical investigators using descrip
terminology of their own choosing. Consequently, it is not possibl
provide a meaningful estimate of the proportion of individuals experien
adverse events without first grouping similar types of untoward events
a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary te
nology has been used to classify reported adverse events. The frequen
presented, therefore, represent the proportion of the 5,600 Pro
exposed individuals who experienced an event of the type cited on at l
one occasion while receiving Prozac. All reported events are incl
except those already listed in tables, those COSTART terms so general
be uninformative, and those events where a drug cause was remote.
important to emphasize that, although the events reported did occur du
treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enu
ated in order of decreasing frequency using the following definiti
frequent adverse events are defined as those occurring on one or m
occasions in at least 1/100 patients; infrequent adverse events are th
occurring in 1/100 to 1/1,000 patients; rare events are those occurrin
less than 1/1,000 patients.

Body as a Whole—*Frequent*: chills; *Infrequent*: chills and fever, cyst,
edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity,
pelvic pain; *Rare*: abdomen enlarged, cellulitis, hydrocephalus, hypot
mia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System—*Infrequent*: angina pectoris, arrhythmia, h
orrhage hypertension, hypotension, migraine, postural hypotension,
cope, and tachycardia; *Rare*: AV block (first-degree), bradycar
bundle-branch block, cerebral ischemia, myocardial infarct, thr
bophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—*Frequent*: increased appetite; *Infrequent*: aphth
stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glo
tis, liver function tests abnormal, melena, stomatitis, and thirst; *R*
bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, er
itis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hy
chlorhydria, increased salivation, jaundice, liver tenderness, mo
ulceration, salivary gland enlargement, stomach ulcer, tongue dis
oration, and tongue edema.

Endocrine System—*Infrequent*: hypothyroidism; *Rare*: goiter and hy
thyroidism.

Hemic and Lymphatic System—*Infrequent*: anemia and lymphaden
athy; *Rare*: bleeding time increased, blood dyscrasia, leukopenia, l
phocytosis, petechia, purpura, sedimentation rate increased, and thr
bocythemia.

Metabolic and Nutritional—*Frequent*: weight loss; *Infrequent*: ge
alized edema, hypoglycemia, peripheral edema, and weight gain; *Ra*
dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipen
hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficie
anemia.

Musculoskeletal System—*Infrequent*: arthritis, bone pain, bursi
tenosynovitis, and twitching; *Rare*: bone necrosis, chondrodystrop
muscle hemorrhage, myositis, osteoporosis, pathological fracture, a
rheumatoid arthritis.

Nervous System—*Frequent*: abnormal dreams and agitation; *In*
quent: abnormal gait, acute brain syndrome, akathisia, amnesia, apat
ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusio
depersonalization, emotional lability, euphoria, hallucinations, hostil
hyperkinesia, hypesthesia, incoordination, libido increased, manic re
tion, neuralgia, neuropathy, paranoid reaction, psychosis, and verti
Rare: abnormal electroencephalogram, antisocial reaction, chronic br
syndrome, circumoral paresthesia, CNS depression, coma, dysarthi
dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus,
stagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System—*Frequent*: bronchitis, rhinitis, and yawn; *Inf*
quent: asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Ra*
apnea, hemoptysis, hypoxia, laryngx edema, lung edema, lung fibros
alveolitis, and pleural effusion.

Skin and Appendages—*Infrequent*: acne, alopecia, contact dermati
dry skin, herpes simplex, maculopapular rash, and urticaria. *Ra*
eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutis
psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, s
hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—*Infrequent*: amblyopia, conjunctivitis, ear pain,
pain, mydriasis, photophobia, and tinnitus. *Rare*: blepharitis, catara
corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, p
sis, strabismus, and taste loss.

Urogenital System—*Infrequent*: abnormal ejaculation, amenorrh
breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrh
menopause, menorrhagia, ovarian disorder, urinary incontinence, urin
retention, urinary urgency, urination impaired, and vaginitis; *Rare*: ab
tion, albuminuria, breast enlargement, dyspareunia, epididymitis, fem
lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhag
orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, u
thritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uter
spasm, and vaginal hemorrhage.

Overdosage: *Human Experience*—As of December 1987, there were t
deaths among approximately 38 reports of acute overdose with fluoxeti
either alone or in combination with other drugs and/or alcohol. One dea
involved a combined overdose with approximately 1,800 mg of fluoxet
and an undetermined amount of maprotiline. Plasma concentrations
fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respectively
second death involved three drugs yielding plasma concentrations
follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.
mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine expe
enced two grand mal seizures that remitted spontaneously without speci
anticonvulsant treatment (*see* Management subsection). The acti
amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving hig
fluoxetine doses. Other prominent symptoms of overdose included agi
tion, restlessness, hypomania, and other signs of CNS excitation. Exc
for the two deaths noted above, all other overdose cases recovered witho
residua

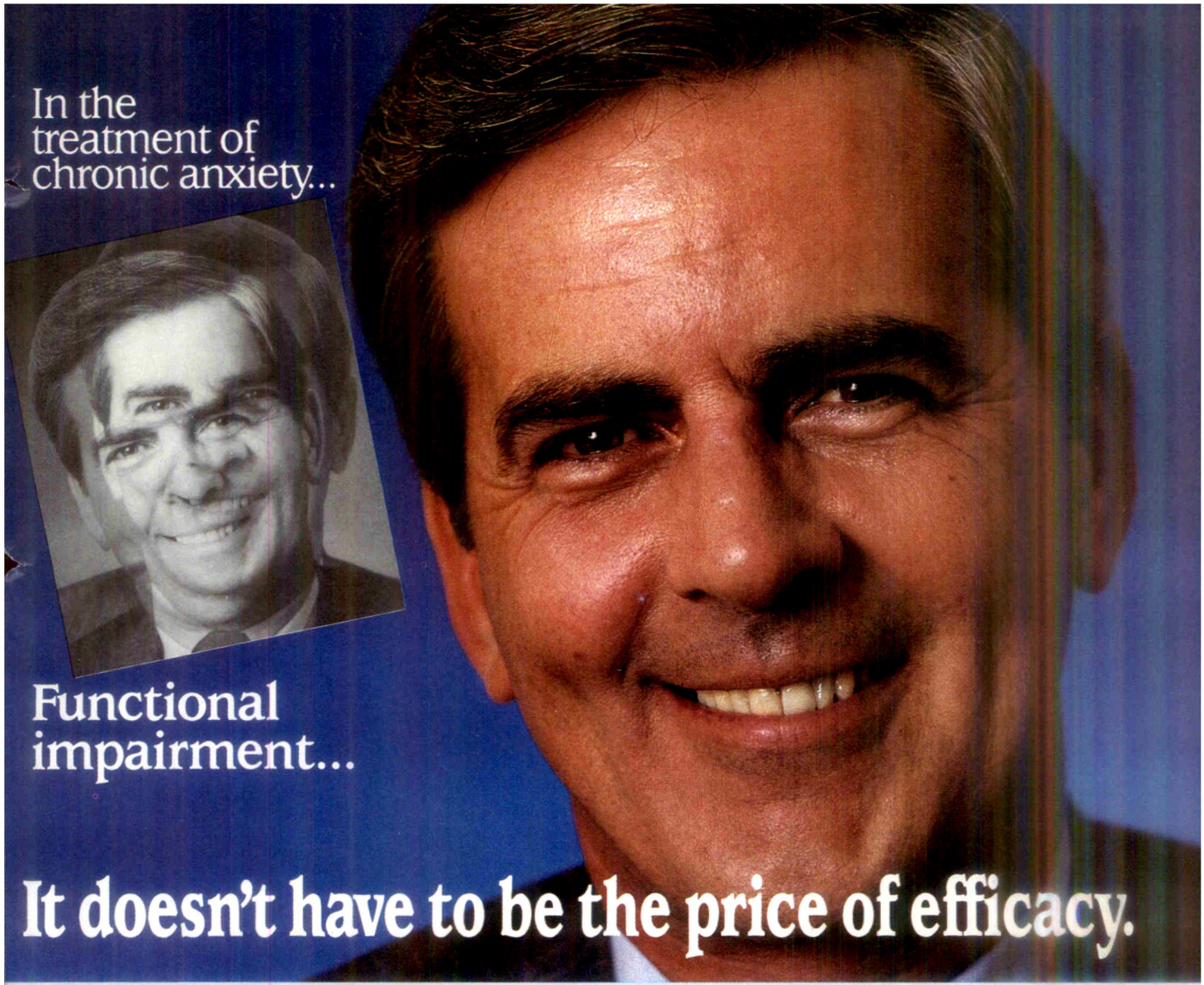
PV 2150 DPP

Additional information available to the profession on request from

Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285

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FL-4903-T-849354



BuSpar relieves anxiety and returns your patient to normal activity

...without significant impairment of psychomotor function*[1-4]

...without producing a benzodiazepine withdrawal syndrome[5] upon discontinuation

Well tolerated—Side effects associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

The first choice for chronic anxiety

BuSpar®
(buspirone HCl)



Tablets, 5 mg and 10 mg

for a different kind of calm

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For Brief Summary, please see following page.

BuSpar® (buspirone HCl)

References: 1. Moskowitz H, Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. *J Clin Psychiatry* 1982;43(12, Sec 2):45-55. **2.** Goa K L, Ward A: Buspirone—A preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. *Drugs* 1986;32:114-129. **3.** Lader M: Buspirone: Psychomotor effects vs. benzodiazepines. Proceedings from Anxiety Disorders: An International Update, 1986, pp 71-78. **4.** Moskowitz H: Buspirone: Effect on driving skills vs. benzodiazepines. Proceedings from Anxiety Disorders: An International Update, 1986, pp 83-86. **5.** Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26.

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: *General*—*Interference with cognitive and motor performance:*** Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (i.e., represent akathisia).

***Information for Patients*—**Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only if clearly needed.

***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.

***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of age.

***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

***Incidence in Controlled Clinical Trials*—**Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

***Other Events Observed During the Entire Pre-marketing Evaluation*—**The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

***Physical and Psychological Dependence*—**Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

***Recommended Overdose Treatment*—**General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

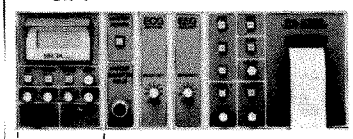
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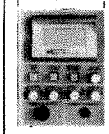
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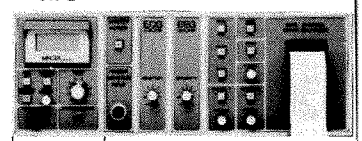


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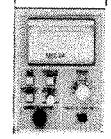
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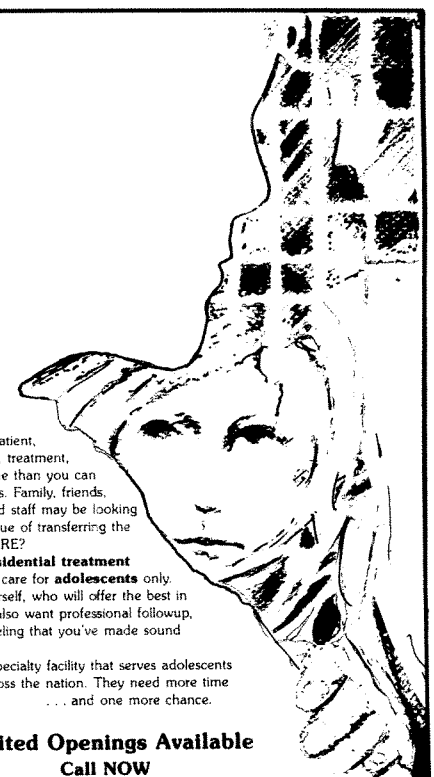
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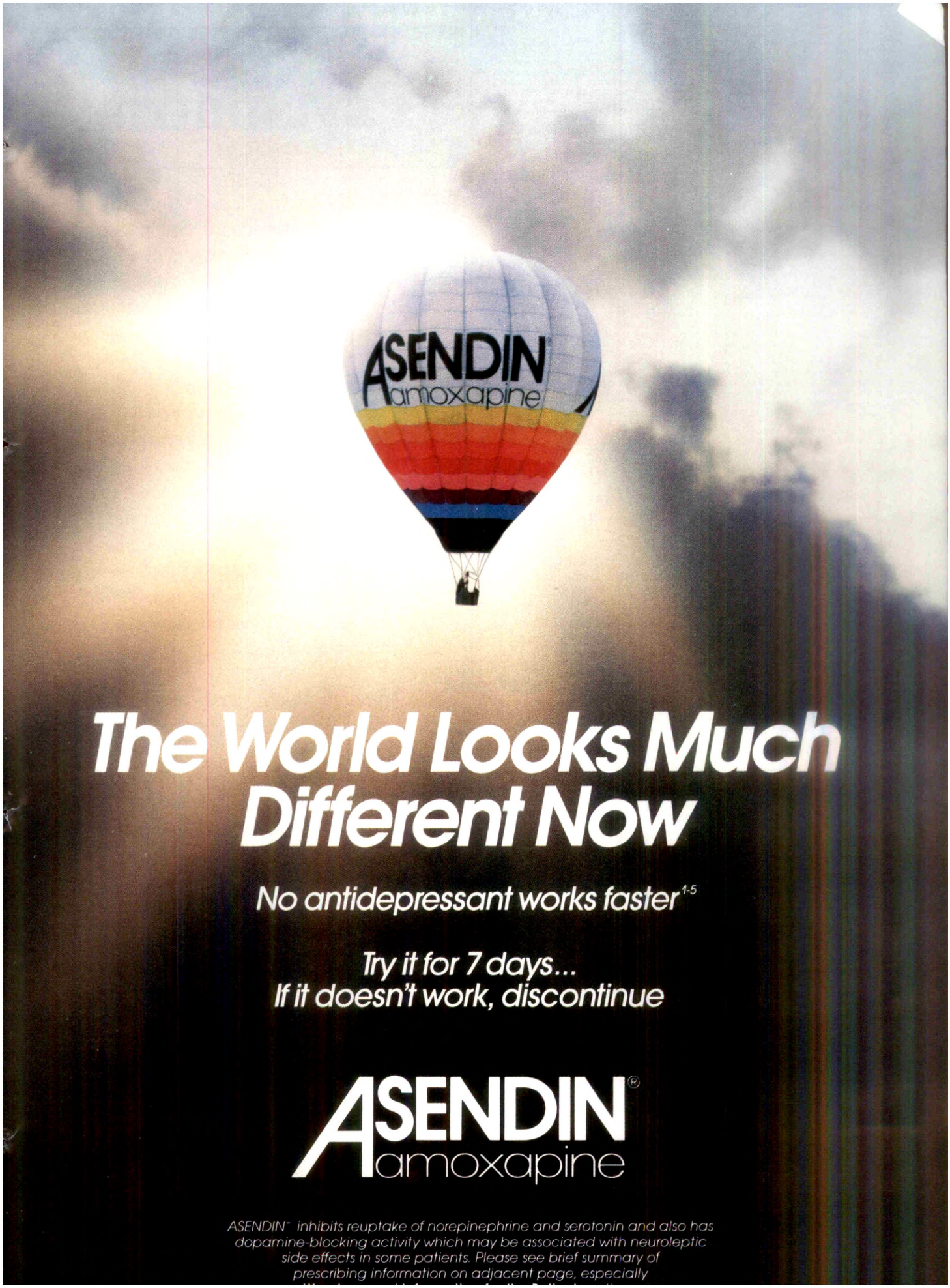
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amoxapine

ASENDIN® inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects in some patients. Please see brief summary of prescribing information on adjacent page, especially

ASENDIN® amoxapine

BRIEF SUMMARY
ASENDIN® amoxapine Tablets, 25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY: *ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.*

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. In vitro tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS: *ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.*

CONTRAINDICATIONS: *Prior hypersensitivity to dibenzoxazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN® amoxapine, allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.*

WARNINGS: Tardive Dyskinesia: *Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.*

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.)

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: *Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN® amoxapine should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in < 1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported.* Information for the patient: *It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired.* Drug interactions: *See Contraindications regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered.* Therapeutic interactions: *Concurrent administration with electroshock may increase hazards associated with such therapy.* Carcinogenesis, impairment of fertility: *In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length.* Pregnancy. Pregnancy Category C. *Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.* Nursing mothers: *ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women.* Pediatric use: *Safety and effectiveness in children below the age of 16 have not been established.*

ADVERSE REACTIONS: *Reported in Controlled Studies:* Incidence greater than 1%—*Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).*

Less frequently reported reactions were: CNS and Neuromuscular—*anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns.* Allergic—*edema, skin rash.* Endocrine—*elevation of prolactin levels.* Gastrointestinal—*nausea.* Other—*dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration.* Incidence less than 1%—Anticholinergic—*disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness.* Cardiovascular—*hypotension, hypertension, syncope, tachycardia.* Allergic—*drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis.* CNS and Neuromuscular—*tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported.* Hematologic—*leukopenia, agranulocytosis.* Gastrointestinal—*epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea.* Endocrine—*increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion.* Other—*lacrimation, weight gain or loss, altered liver function.* Drug Relationship Unknown. *Reported rarely, but under circumstances where drug relationship was unknown:* Anticholinergic—*paralytic ileus.* Cardiovascular—*atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block.* CNS and Neuromuscular—*hallucinations.* Hematologic—*thrombocytopenia, eosinophilia, purpura, petechiae.* Gastrointestinal—*parotid swelling.* Endocrine—*change in blood glucose levels.* Other—*pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.*

Additional Adverse Reactions Reported with Other Antidepressant Drugs: Anticholinergic—*sublingual adenitis, dilation of the urinary tract.* CNS and Neuromuscular—*delusions.* Gastrointestinal—*stomatitis, black tongue.* Endocrine—*gynecomastia.*

OVERDOSAGE: Signs and Symptoms

Toxic manifestations of ASENDIN® amoxapine overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.

Treatment

Treatment of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (N Engl J Med 1982; 306: 1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev. 12/85

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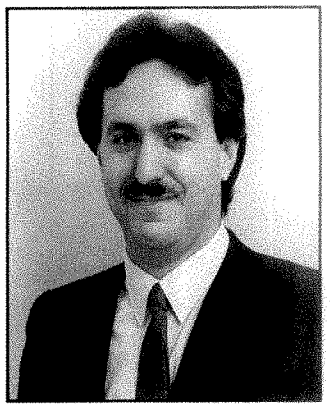
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Thanks To These Researchers, The Future Of Psychiatry Has Never Looked Better.

On May 9, the American Psychiatric Association announced the winners of the second annual Psychiatric Institutes of America Foundation Awards for Hospital Psychiatry Research.

All of us at the Psychiatric Institutes of America Foundation salute Marvin I. Herz, M.D., Gregory R. Baumgartner, M.D., and Michael L. Silver, M.D. for their contributions to research which benefit all psychiatry.

Dr. Herz is professor and chairman of the department of psychiatry at the State University of New York at Buffalo School of Medicine. He is also director of psychiatry at Erie County Medical Center and Buffalo General Hospital. He and his associates were among the first researchers to identify early predictors of relapse among schizophrenic patients.

Dr. Baumgartner and Dr. Silver are both psychiatric residents. Dr. Baumgartner, a 1984 graduate of the University of Ottawa School of Medicine, is currently completing his fourth year of residency at the University of South Carolina William S. Hall Psychiatric Institute. His years of research have aided hospital physicians in the use of psychopharmacological drugs in the treatment of chemically-dependent patients.

Dr. Silver is currently completing his psychiatric residency at NYU Medical Center. A fellowship with Luis R. Marcos, M.D., led to a study on the management styles of psychiatrist administrators. This study demonstrated ways in which administrators may improve patient clinical care given resource constraints.

Psychiatric Institutes of America is delighted that these three researchers were so honored. The entire field of psychiatry shares in the rewards of their research.

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Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

AUGUST

August 1–6, annual meeting, International Transactional Analysis Association, Rio de Janeiro. Contact Susan Sevilla, Executive Director, 1772 Vallejo St., San Francisco, CA 94122; 415-885-5992.

August 4–11, annual meeting, American Bar Association, Toronto. Contact Thomas H. Gonser, Esq., Executive Director, 750 North Lake Shore Dr., Chicago, IL 60611; 312-988-5130.

August 6–9, annual meeting, National Depressive and Manic Depressive Association, Detroit. Contact Marilyn Weiss, President, Merchandise Mart, Box 3395, Chicago, IL 60654; 312-993-0066.

August 6–12, annual meeting, American Institute of Biological Sciences, Davis, Calif. Contact Dr. Charles M. Chambers, Executive Director, 730 11th St., N.W., Washington, DC 20001-4584; 202-628-1500.

August 8–10, annual meeting, American Hospital Association, New Orleans. Contact Denise Koumiss, 840 North Lake Shore Dr., Chicago, IL 60611; 312-280-6000.

August 12–16, annual meeting, American Psychological Association, Atlanta. Contact Leonard D. Goodstein, Ph.D., Executive Officer, 1200 17th St., N.W., Washington, DC 20036; 202-955-7660.

August 13–19, 11th International Congress of Hypnosis and Psychosomatic Medicine, Leiden/The Hague, The Netherlands. Contact Congress Secretariat, P.O. Box 16065, 2301 GB Leiden, The Netherlands; 071-275294.

August 21–24, XVIth C.I.N.P. Congress, Neurochemical Correlates of Affective Disorders and Their Treatment, Copenhagen. Contact Dr. A. Geisler, Dept. of Pharmacology, University of Copenhagen, 20 Juliane Maries Vej, DK-2100 Copenhagen, Denmark; 1-37-03-75.

August 21–25, 8th International Congress of International Association for the Scientific Study of Mental Deficiency, Dublin. Contact Mr. John O'Gorman, Congress Chairman, 8th World Congress, I.A.S.S.M.D., 12, Pembroke Park, Dublin 4, Ireland.

August 23–28, annual meeting, American Association for Partial Hospitalization, Denver. Contact Joan Fridberg, Administrative Coordinator, 1221 Massachusetts Ave., N.W., Suite 3, Washington, DC 20005; 202-347-1649.

August 24–28, annual meeting, American Sociological Association, Atlanta. Contact Jen L. Suter, Meetings and Marketing Manager, 1722 N St., N.W., Washington, DC 20036; 202-833-3410.

August 30–September 4, XXXI International Congress on the History of Medicine, Bologna, Italy. Contact Organizing Secretariat, Conference Service, Via Tagliapietre, 18/B, 40123 Bologna, Italy; 051-331466; Telex 213616 BO I.

SEPTEMBER

September 4–9, 10th International Congress on Criminology, Hamburg, F.R.G. Contact Congress Secretariat, HMC Congress Organisation, 10th Int. Congr. Crimin., P.O. Box 30 24 80, D–2000 Hamburg 36, F.R.G.; 040-35-69-22-42; Telex 212 609, Telefax 35 69 21 80.

September 4–9, 17th European Conference on Psychosomatic Research, Marburg, West Germany. Contact Prof. Dr. med. Wolfram Schuffel, Psychosomatic Division, Centre of Internal Medicine, University of Marburg, D-2550 Marburg, West Germany.

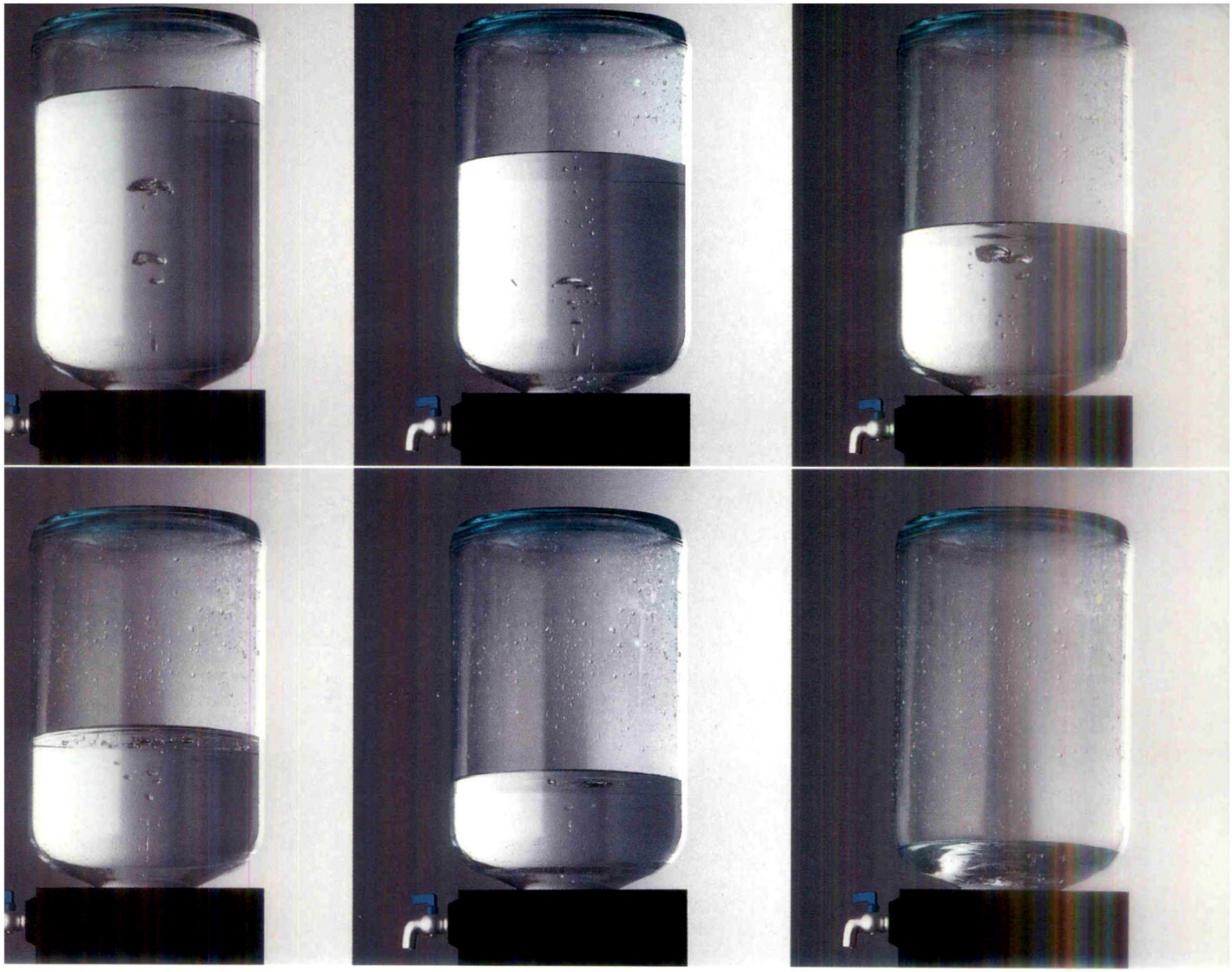
September 5–10, Behaviour Therapy World Congress '88, Edinburgh. Contact Rod Holland, Congress Coordinator, Congress Workshops, WCBT '88, 59 Heath Gardens, Twickenham, Middlesex TW1 4LY, England UK.

September 7–11, Fall Components Meeting, American Psychiatric Association, Washington, D.C.

September 12–17, IVth International Conference of Psychophysiology, Prague. Contact Association of Czechoslovak Medical Societies, J.E. Purkyne, IVth I.C.P., P.O. Box 88, CS–120 26 PRAHA 2, Czechoslovakia; Telex 121293.

September 14–17, Fourth International Conference of the Marce Society, The Family, Childbearing and Mental Illness, University of Keele, England. Contact Marce Society Secretariat, Bell Howe Conferences, Gothic House, Barker Gate, Nottingham, NG1 1JU, England; 0602-410679.

(Continued on page A37)



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References: 1. Thompson TL, Thompson WL: Treating depression: Tricyclics, tetracyclics, and other options. *Modern Medicine* 1983;51(8):87-109. **2.** Georgotas A: Affective disorders: Pharmacotherapy, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry IV.* Baltimore, Williams & Wilkins, 1985, vol 1, pp 821-833. **3.** Bye C, Clubley M, Peck AW: Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol* 1978;6:155-161. **4.** Roose SP, Glassman AH, Siris SG, et al: Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: A meaningful difference. *J Clin Pharmacol* 1981;1:316-319. **5.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 413-423. **6.** Thayssen P, Bjerre M, Kragh-Sorensen P, et al: Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology* 1981;74:360-364. **7.** Ziegler VE, Clayton PJ, Biggs JT: A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry* 1977;34:607-612.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone-marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage. [PAM-Z13—7/15/86]

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CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity. Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL. Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis. Patients receiving SYMMETREL who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness and motor coordination are important.

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently. Because SYMMETREL is not metabolized and is mainly excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of SYMMETREL should be reduced in patients with renal impairment and in individuals who are 65 years of age or older. The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system stimulants. No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems.

Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women. SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The adverse reactions reported most frequently (5 – 10%) are: nausea, dizziness (lightheadedness), and insomnia. Less frequently (1 – 5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, and constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension and headache. Infrequently (0.1 – 1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, fatigue, skin rash, vomiting, weakness, slurred speech and visual disturbance. Rarely (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis and oculogyric episodes.

OVERDOSAGE: There is no specific antidote. However, slowly administered intravenous physostigmine in 1 and 2 mg doses in an adult* at 1 to 2 hour intervals and 0.5 mg doses in a child† at 5 to 10 minute intervals up to a maximum of 2 mg/hour have been reported to be effective in the control of central nervous system toxicity caused by amantadine hydrochloride. For acute overdosing, general supportive measures should be employed along with immediate gastric lavage or induction of emesis. Fluids should be forced and, if necessary, given intravenously. Hemodialysis does not remove significant amounts of SYMMETREL; in patients with renal failure, a four hour hemodialysis removed 7 to 15 mg after a single 300 mg oral dose.‡ The pH of the urine has been reported to influence the excretion rate of SYMMETREL. Since the excretion rate of SYMMETREL increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase the elimination of the drug from the body. The blood pressure, pulse, respiration and temperature should be monitored. The patient should be observed for hyperactivity and convulsions; if required, sedation and anticonvulsant therapy should be administered. The patient should be observed for the possible development of arrhythmias and hypotension; if required, appropriate antiarrhythmic and antihypotensive therapy should be given. The blood electrolytes, urine pH and urinary output should be monitored. If there is no record of recent voiding, catheterization should be done. The possibility of multiple drug ingestion by the patient should be considered.

DOSAGE AND ADMINISTRATION: Dosage for Drug-induced Extrapyramidal Reactions:
Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

HOW SUPPLIED: SYMMETREL (amantadine hydrochloride) is available as capsules (each red, soft gelatin capsule contains 100 mg amantadine hydrochloride) in:

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References:

1. Borison RL, Diamond BI: Treatment of extrapyramidal side-effects: amantadine versus benztropine. *World J Psychosynthesis* (special issue) 1984-1985; 16:40-43. **2.** McEvoy JP, McCue M, Spring B, et al: Effects of amantadine and trihexyphenidyl on memory in elderly normal volunteers. *Am J Psychiatry* 1987; 144(5):573-577.

* D.E. Casey, *N. Engl. J. Med.* 298:516, 1978.
† C.D. Berkowitz, *J. Pediatr.* 95:144, 1979.
‡ V.W. Horadam, et. al., *Ann. Intern. Med.* 94:454, 1981.

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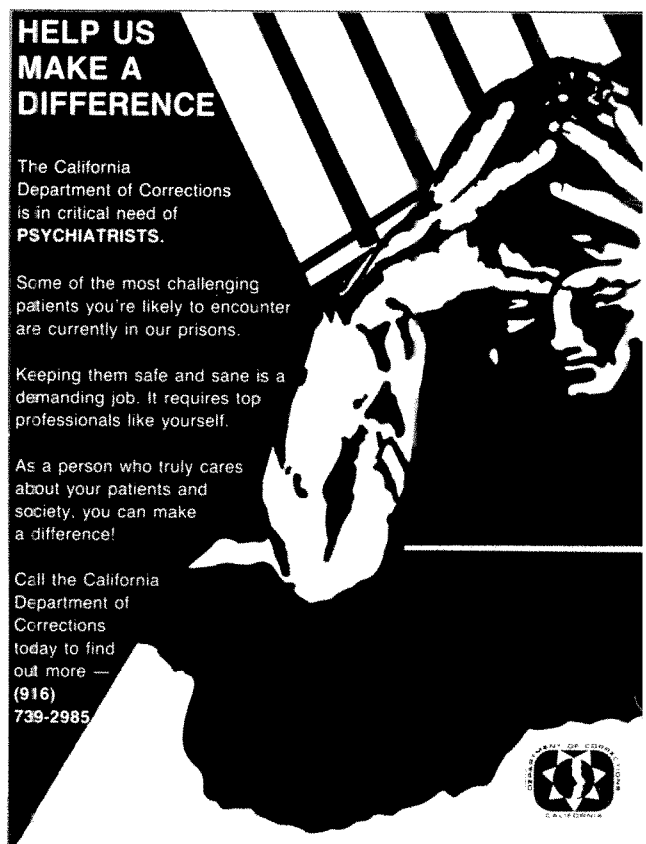
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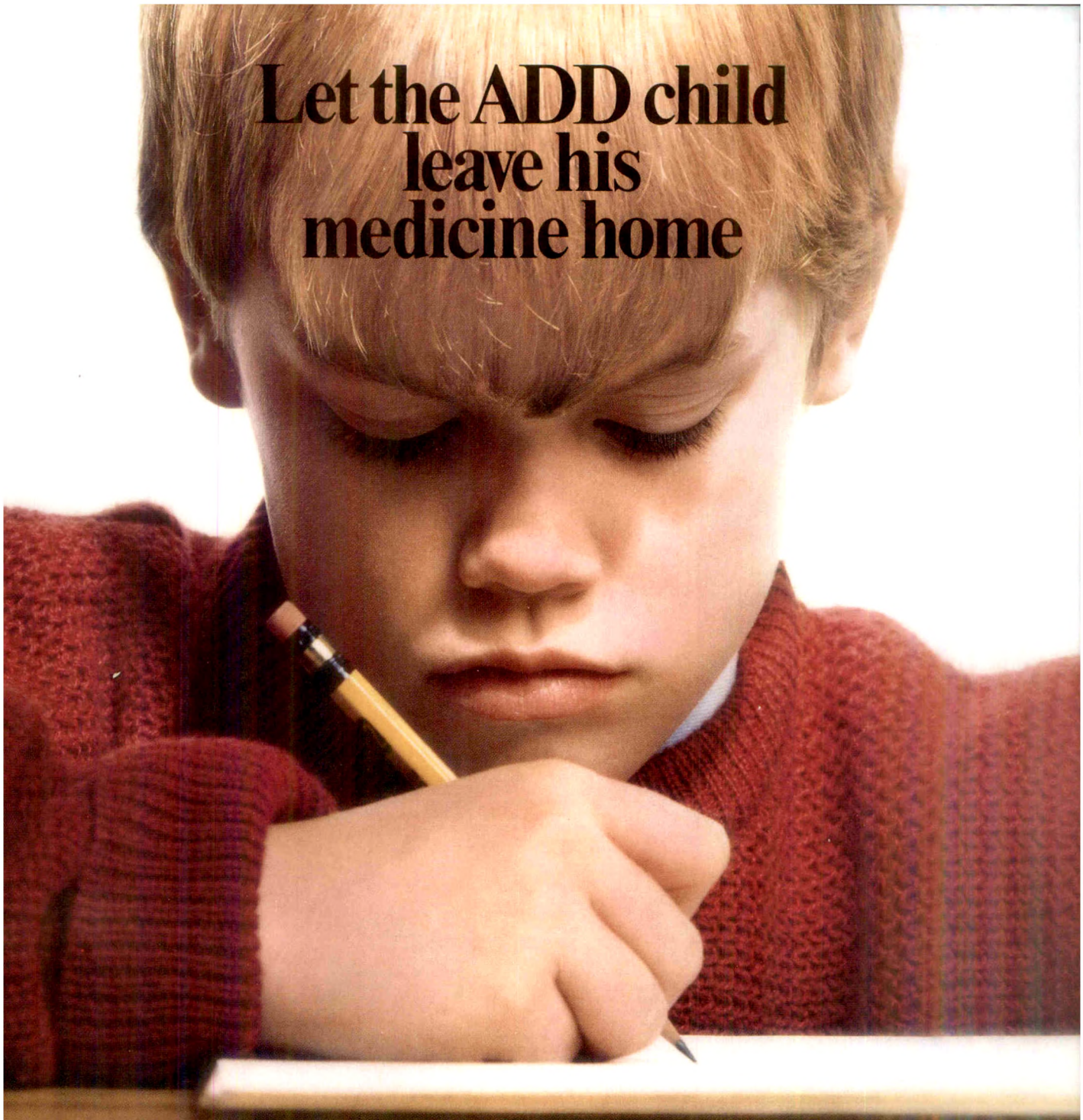
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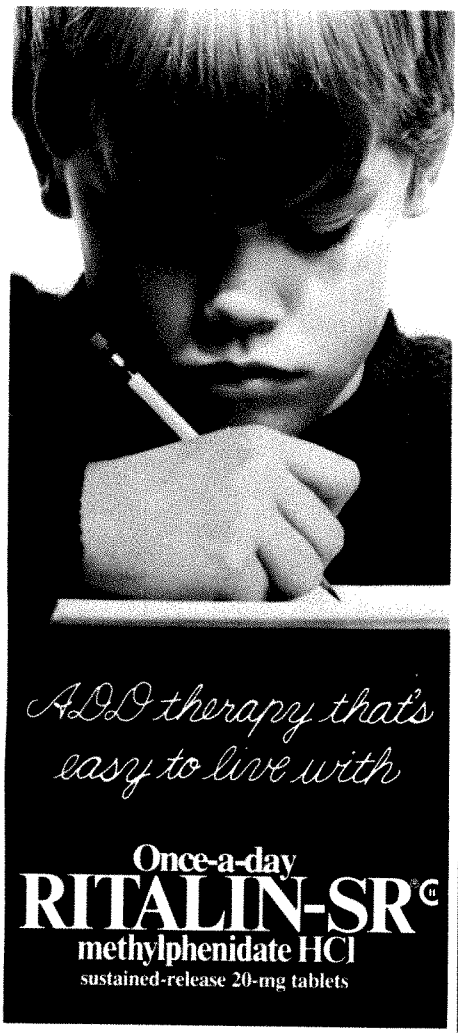
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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS

Attention Deficit Disorders, Narcolepsy

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children). Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

WARNINGS

Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*ie*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic antidepressants (imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Usage in Pregnancy

Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

Adults

Tablets: Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

Children (6 years and over)

Ritalin should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Ritalin should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

OVERDOSAGE

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of emesis or gastric lavage. In the presence of severe intoxication, use a carefully titrated dosage of a *short-acting* barbiturate *before* performing gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Ritalin overdosage has not been established.

HOW SUPPLIED

Tablets 5 mg — round, yellow (imprinted CIBA 7)

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Protect from light.

Dispense in tight, light-resistant container (USP).

SR Tablets 20 mg — round, white, coated (imprinted CIBA 16)

Bottles of 100	NDC 0083-0016-30

Note: SR Tablets are color-additive free.

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Dispense in tight, light-resistant container (USP).

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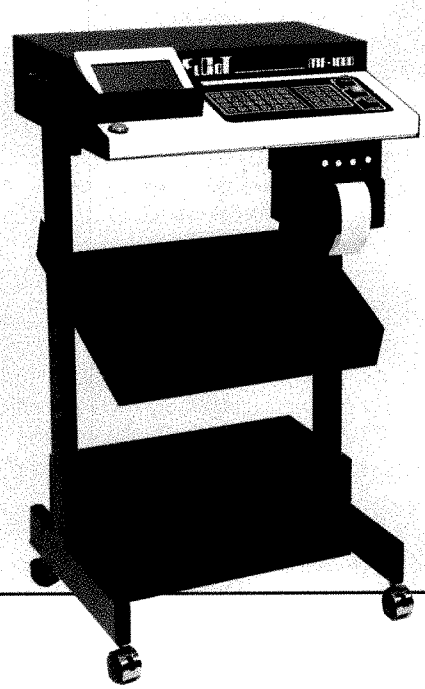
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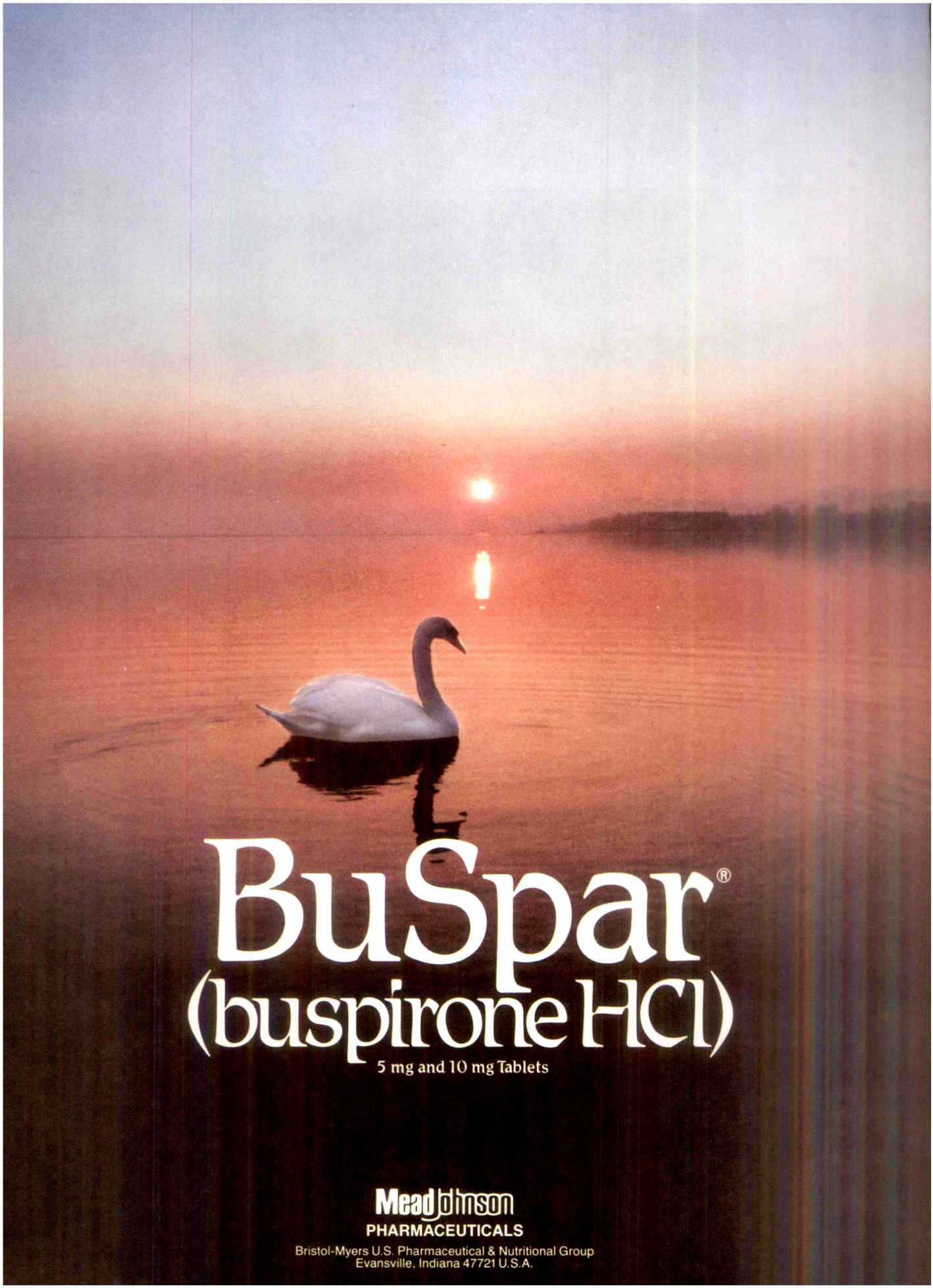
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Indirect Vertical Cultural Transmission: A Model for Nongenetic Parental Influences on the Liability to Psychiatric Illness

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A long tradition in psychiatry has focused on parental traits that directly influence the liability to psychiatric disorders in offspring. Because these traits rarely resemble the disorders they cause, traditional models of cultural transmission (which assume that "like perpetuates like") may not be appropriate. The author develops and illustrates several models for indirect vertical cultural transmission of psychiatric illness. These models generate falsifiable predictions about the pattern of risk in relatives of affected individuals. For example, all such models predict a substantially higher risk of illness in siblings than in offspring of affected individuals. It is now possible to develop and test rigorous models for the cultural transmission of psychiatric illness.

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A long tradition in psychiatry has advocated the importance of intrafamilial psychological factors in the etiology of psychiatric illness. A particular focus has been the behavioral characteristics in parents that predispose to psychiatric disorders in their offspring (e.g., 1–10). Most of this work has assumed that parental "predisposing" behavior which increases the risk in offspring for a specific psychiatric disorder has little relationship to the clinical features of the disorder itself. For example, "schizophrenogenic" behavior ascribed to the parents of schizophrenic patients (e.g., overintrusiveness) (1, 3, 4) bears little resemblance to the clinical features of schizophrenia. Parental characteristics that may predispose to depression in offspring (e.g., overprotectiveness coupled with lack of warmth) (8, 10) have no apparent relationship to clinical depression.

This paper is an attempt to rigorously explore the predictions of this hypothesis for the pattern of intrafamilial transmission of psychiatric disorders. Specifically, it seeks to examine the pattern of risks of illness that would be expected in the close relatives of affected individuals if parental predisposing behaviors were the *major* cause of familial resemblance in risk to psychiatric disorders.

The first step in reaching our goal is to construct a model that captures the critical features of the hypothesized mode of familial transmission. While several models for the environmental transmission of traits from parents to offspring (termed "vertical cultural transmission") have been proposed (11–14), nearly all of them assume that a parental trait directly influences the offspring to acquire that same trait (e.g., "like perpetuates like"). For example, intelligent parents, by providing a stimulating environment, may tend to produce intelligent offspring. Such a model can be termed "direct vertical cultural transmission."

By contrast, most theories of the cultural transmission of psychiatric disorders postulate that parental characteristics which predispose to a certain psychiatric disorder are quite distinct from the characteristics of the disorder itself. This can be termed "indirect vertical cultural transmission." In this paper, I will outline and illustrate the expected results of four mod-

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els that include the indirect vertical cultural transmission of the liability to psychiatric illness.

THE MODELS

The models focus on the interrelationship within individuals and within families of two behavioral "syndromes" that shall be termed "predisposing traits" and "disorder." The relevant predisposing trait is assumed to be a quantitative, normally distributed variable, while the disorder is a dichotomous trait, which can be conceptualized in a "liability-threshold" framework (15). That is, underlying the disorder is a normally distributed latent liability with a single threshold such that only individuals with liabilities above the threshold are affected.

The expected correlations for predisposing traits and liability to the disorder between relatives are derived by path analysis, a statistical method for representing a hypothesized causal network between latent and observed variables (16, 17). Path coefficients have a strict statistical meaning: "one-headed" arrows represent standardized partial regression coefficients (I will here use the term "direct effect" for this kind of path), and "two-headed" arrows are correlation coefficients. On a more intuitive level, a path diagram depicts a hypothesized pattern and direction of effects within a set of interrelated variables. When well-established rules are used, the predicted correlation between variables in a path diagram can be determined by adding all the "paths" that connect them (16). The risk in relatives for the disorder can then be calculated, by using previously derived formulae (18, 19), from 1) the correlation of liability to the disorder between relatives, and 2) the threshold for the disorder, which is derived from the postulated population prevalence.

In the illustrations of the model, I will assume a population risk for the disorder of 1%. To demonstrate that useful information about cultural transmission can be obtained from the study of common relationships, the models will be illustrated for intact nuclear and extended families. However, all of the models outlined could be extended to other, rarer relationships commonly used in psychiatric genetic research (e.g., twins and adoptees). Throughout this presentation, it will be assumed that there are neither genetic nor sex-related environmental influences on predisposing traits or liability to the disorder.

For brevity, I will use the male gender to refer to relations that could be male or female (e.g., uncle/aunt-niece/nephew becomes uncle-nephew). When referring to risks for parallel relationships in ancestors and descendants, I will refer to descendants only (e.g., parents or offspring become offspring, and uncles or nephews become nephews). While the illustrations of the models reported were broadly representative of what would be expected from the models under "reasonable" parameter values, this paper should not be construed as an exhaustive review of results of these models. Given the technical nature of some of the following comments, key points are summarized in italics.

TABLE 1. Predicted Correlations Between Relatives in Liability to the Disorder Under Various Models for Indirect Vertical Cultural Transmission of Psychiatric Illness[a]

Model[b]	Predicted Correlation[c]			
	Parents or Offspring	Siblings	Uncles or Nephews	Grandparents or Grandchildren
IVCT L(D)	0	$2b^2$	0	0
IVCT L(D) DVCT P	$2ab^2$	$2b^2$	$2ab^2$	$2a^2b^2$
IVCT L(D) DVCT P SC P	$2ab^2(1+d)^2$	$2b^2(1+d)$	$2ab^2(1+d)^2$	$2a^2b^2(1+d)^3$
DVCT L(D)	f	$2f^2$	$2f^3$	f^2
IVCT L(D)[d] DVCT P DVCT L(D)	bc+f	$2b^2+4bcf+2f^2$	$2ab^2+2abcf+4bcf^2+2b^2f+2f^3$	$abc+bcf+f^2$

[a]These and other correlations presented in this paper assume equilibrium conditions.

[b]IVCT=indirect vertical cultural transmission, DVCT=direct vertical cultural transmission, L(D)=liability to the disorder, P=predisposing traits, and SC=spousal correlation.

[c]a=the direct effect of P in a parent on P in his offspring, b=the direct effect of P in a parent on the liability to D in his offspring, c=the correlation within individuals of P and the liability to D, d = the correlation in P between spouses, and f=the direct effect of the liability to D in a parent on his offspring.

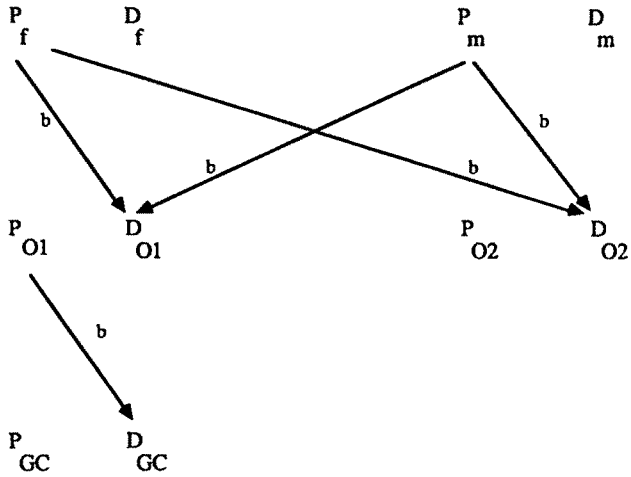
[d]$c=\frac{2ab}{1-2af}$.

Each of the individual models considered here will generate an array of predicted correlations for predisposing traits and liability to the disorder within and between relatives. All of these expected correlations are available from the author on request. The emphasis here will be to examine the predicted correlations in liability to the disorder between relatives (table 1) and then to translate these correlations into risk figures. The reader is advised to pay attention not to the specific correlations or risk figures, *but rather to the pattern of correlations and risks in the four major categories of relatives considered: offspring, siblings, nephews, and grandchildren.* As will become clear, the particular pattern of correlations and/or risks is a constant feature of the individual models. Finally, to increase comprehensibility, I will include for each model an example in which it is assumed (for purposes of illustration only) that intrusiveness is the parental predisposing trait and schizophrenia the disorder of interest.

Indirect Vertical Cultural Transmission for Liability to the Disorder Only

The first model assumes that the only source of resemblance between relatives for liability to the dis-

FIGURE 1. The Simplest Model for Indirect Vertical Cultural Transmission of Psychiatric Illness[a]



[a]The diagram depicts the predicted relationship between predisposing traits (P) and the disorder (D) in father (*f*), mother (*m*), two offspring (01 and 02), and one grandchild (GC) who is 1) a grandchild of father and mother, 2) a child of offspring 01, and 3) a nephew of offspring 02. This model includes only a single path coefficient: *b*—the direct effect of P in a parent on the liability to D in his offspring.

order is indirect vertical cultural transmission for liability to the disorder. *Example*: The only source of familial resemblance for the liability to schizophrenia is that intrusiveness in parents affects the liability to schizophrenia in their offspring. In terms of path analysis, this model suggests that only a single path, which will be termed *b*, exists between relatives. This path is formally defined as:

> *b*—the direct effect of predisposing traits in a parent on liability to the disorder in his offspring.

The relationship between liability to the disorder and predisposing traits in two parents, two offspring, and a grandchild in this first model is seen in figure 1. The correlations in liability for the disorder between relatives predicted by this model are seen in table 1 (first row). As is clear from an inspection of the path diagram, in this model only siblings will be correlated for liability to the disorder. This is true because siblings will be exposed to the same parental predisposing traits. No parent-offspring transmission for liability to the disorder will occur in this model.

Table 2 shows the expected risk for the disorder in relatives of affected individuals for this model when *b* equals 0.3 and 0.5. The risks of illness in offspring, nephews, and grandchildren of affected individuals do not exceed the population expectation for illness of 1.0%. In this model, the risk for the disorder is increased only in siblings and equals 3.0% and 12.9%, respectively, for the two values of *b*.

If the only source of resemblance between relatives is the tendency for predisposing traits in parents to cause illness in offspring, then the only category of relatives of affected individuals who will have an increased risk of illness will be siblings.

The Addition of Direct Vertical Cultural Transmission for Predisposing Traits

It is plausible that the parental predisposing traits could themselves be directly transmitted from parents to offspring. That is, individuals will tend to treat their children as they themselves were treated as children. For example, individuals who were abused as children may be at increased risk for abusing their own children when they become parents (20). This model therefore includes indirect vertical cultural transmission for liability to the disorder *and* direct vertical cultural transmission for predisposing traits. *Example*: In this model, there are two sources of familial resemblance for liability to schizophrenia; intrusiveness in parents affects 1) the liability to schizophrenia in their offspring and 2) the level of intrusiveness their children will demonstrate when they themselves become parents. Direct vertical cultural transmission for predisposing traits will be expressed by the path *a*, formally defined as:

> *a*—the direct effect of predisposing traits in a parent on predisposing traits in his offspring.

One interesting property of this model, pictured in figure 2, is that it results in a correlation, within individuals, between predisposing traits and liability to the disorder. This correlation, expressed by the double-headed arrow *c*, can be shown to be equal to $2ab$ and is formally defined as:

> *c*—the correlation within individuals between predisposing traits and liability to the disorder.

The correlation within individuals between predisposing traits and liability to the disorder in this model is best illustrated by the following example: parents with high levels of intrusiveness will tend to produce offspring with high levels of both intrusiveness and liability to schizophrenia. Parents with low levels of intrusiveness will tend to produce offspring with low levels of both intrusiveness and liability to schizophrenia.

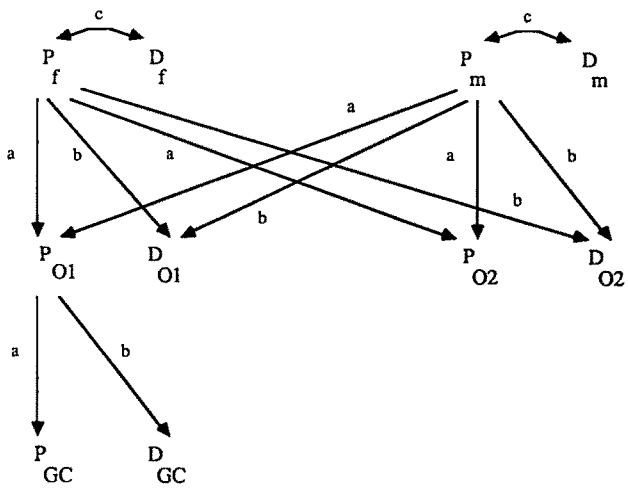
The correlations in liability to the disorder in relatives that are predicted by this model are seen in table 1 (second line). Three results are worthy of note. First, siblings will always be more highly correlated for liability to the disorder than are parents and offspring. In fact, the ratio of the correlation in liability to the disorder between siblings and parent-offspring pairs will always equal exactly $1/a$, the inverse of the value of the path for the direct transmission of predisposing traits. Second, the correlation in liability to the disorder will always be equal in parent-offspring and uncle-nephew pairs. Third, uncle-nephew pairs will always be more highly correlated for liability to the disorder

TABLE 2. Predicted Risk for the Disorder in Relatives of Affected Individuals Under Various Models of Indirect Vertical Cultural Transmission of Psychiatric Illness[a]

Model	Path Coefficients[b]			Risk (%)			
	a	b	d	Parents or Offspring	Siblings	Uncles or Nephews	Grandparents or Grandchildren
IVCT L(D)	0.0	+0.3	—	1.0	3.0	1.0	1.0
	0.0	+0.5	—	1.0	12.9	1.0	1.0
IVCT L(D)	+0.3	+0.3	—	1.4	3.0	1.4	1.1
DVCT P	+0.3	+0.5	—	2.6	12.9	2.6	1.4
	+0.5	+0.5	—	4.4	12.9	4.4	2.2
IVCT L(D)	+0.3	+0.5	0.0	2.6	12.9	2.6	1.4
DVCT P	+0.3	+0.5	+0.2	3.7	18.8	3.7	1.7
SC P	+0.3	+0.5	+0.4	5.4	26.9	5.4	2.6

[a]The predicted risk assumes that the population risk for the disorder equals 1.0%.
[b]See table 1 for definition of path coefficients.

FIGURE 2. The Second Model of Indirect Vertical Cultural Transmission of Psychiatric Illness With Addition of Direct Vertical Cultural Transmission of Predisposing Traits (P)[a]



[a]This model includes three path coefficients: *a*—the direct effect of P in a parent on P in his offspring, *b*—the direct effect of P in a parent on the liability to D in his offspring, and *c*—the correlation within individuals of P and the liability to D. Otherwise, all other abbreviations are as in figure 1.

than are grandparent-grandchild pairs (also by a ratio of $1/a$).

To illustrate this model, the predicted risks for the disorder in relatives of affected individuals were calculated under three conditions: a=b=0.3, a=0.3 and b=0.5, and a=b=0.5 (table 2). In each case, 1) the risk of illness is considerably greater in siblings than in offspring of affected individuals, 2) the risk of illness is equal in offspring and nephews, and 3) the risk in nephews exceeds that found in grandchildren. Also, the difference in the risk in siblings and offspring and in nephews and grandchildren becomes less as the correlation for the predisposing traits between parents and offspring increases. *This model predicts that the pattern of risks of illness in relatives of affected probands will always have the following order: siblings> offspring=nephews>grandchildren.*

The Addition of Spousal Correlations for Predisposing Traits

It is plausible that spouses may be correlated in their levels of predisposing traits. For example, an individual might choose a spouse with a similar level of predisposing traits (e.g., individuals with a cold, overprotective parental style may tend to marry individuals with a similar approach to childrearing). Alternatively, during the course of marriage individuals may tend to influence one another to develop similar parenting styles. *Example*: This model is just like the preceding one with the addition that spouses are now assumed to be correlated for levels of intrusiveness. In either case, we can model this effect by introducing a new path coefficient:

> *d*—the correlation in predisposing traits between spouses.

The path diagram for the previous model can be modified by the inclusion of this new path (not shown; available from the author). The expected correlations in liability to the disorder between relatives derived therefrom are seen in table 1 (third line).

The addition of a spousal correlation for predisposing traits results in a pattern of correlations quite similar to that found in the previous model. Specifically, the correlations for liability to the disorder remain 1) much higher in siblings than in parent-offspring pairs, 2) equal in parent-offspring and uncle-nephew pairs, and 3) much higher in uncle-nephew than in grandparent-grandchild pairs. However, the ratio between sibling/parent-offspring and uncle-nephew/grandparent-grandchild correlations now equals $1/[a(1+d)]$.

When a=0.3 and b=0.5, table 2 shows the expected risks for the disorder in relatives for values of *d* from 0 to +0.4. (Correlations found between spouses for some important traits are height, +0.2 to +0.3; personality measures, 0 to +0.3; and intelligence, +0.4 to +0.5 [21].) As the value of *d* increases, the predicted risk of illness in relatives rises. However, regardless of the value of *d*, the overall pattern of risk for illness closely resembles that seen in the previous model. *With the addition to the previous model of spousal correlations for the predisposing traits, the model continues to predict that the risk of illness in relatives of affected probands will always have the following order: siblings>offspring=nephews>grandchildren.*

The Addition of Direct Vertical Cultural Transmission for Liability to the Disorder

The previous models all assumed that the only direct effect that parents have on the liability of their offspring to develop illness is through the parental level of predisposing traits. This indirect vertical cultural transmission is implied in most of the literature that deals with the intrafamilial psychological transmission of psychiatric illness (1–10).

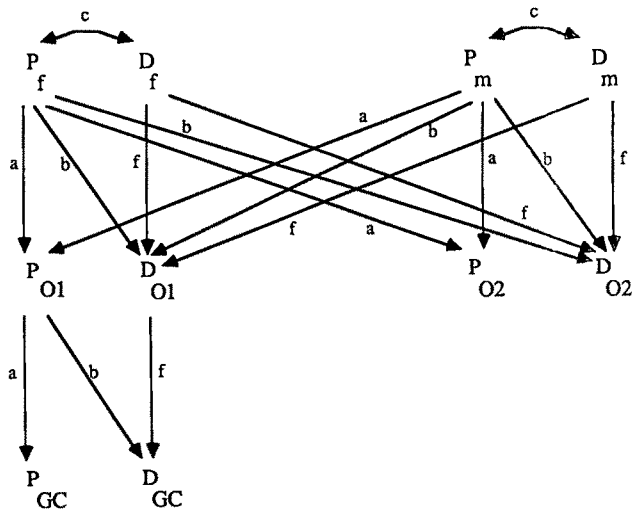
However, it is instructive to examine the impact of including in our model direct vertical cultural transmission for liability to the disorder. Although the concept is rarely emphasized in the psychiatric literature, it is plausible that children may directly acquire, by "social learning," their parents' pathological behavior (22). *Example*: This model includes three major sources of resemblance between relatives for liability to schizophrenia. First, the parental level of intrusiveness directly affects the liability to schizophrenia in the offspring. Second, the parental level of intrusiveness directly influences the level of intrusiveness in offspring. Third, the liability to schizophrenia in parents directly affects the liability to schizophrenia in offspring. Direct vertical cultural transmission for liability to the disorder can be included by adding a new path to the second model (figure 3):

> *f*—the direct effect of liability to the disorder in a parent on liability to the disorder in his offspring.

In order to understand the results of this model, it is helpful initially to examine the expected correlations for liability to the disorder and the associated predicted pattern of risk for the illness in relatives of affected individuals when direct vertical cultural transmission for liability to the disorder is the only source of resemblance between relatives (i.e., a=b=0) (table 1, fourth line; table 3, upper section). Under most realistic circumstances, when the regression of liability to the disorder in offspring on the liability to the disorder of their parents is less than 0.5 (e.g., f<0.5), this pattern is quite different from that predicted by models with indirect transmission. *Under most circumstances, models for direct vertical cultural transmission of liability to the disorder predict that the risk of illness in relatives of affected probands will have the following order: offspring>siblings>grandchildren>nephews.*

When the path for direct vertical cultural transmission from parent to offspring equals exactly 0.5, then the pattern of risk of illness in relatives of affected individuals (offspring=siblings>nephews=grandchildren) still dif-

FIGURE 3. The Fourth Model of Indirect Vertical Cultural Transmission of Psychiatric Illness With Addition of Direct Vertical Cultural Transmission for Liability to the Disorder[a]



[a]This model includes four path coefficients: *a*—the direct effect of P in a parent on P in his offspring, *b*—the direct effect of P in a parent on the liability to D in his offspring, *c*—the correlation within individuals of P and the liability to D, and *f*—the direct effect of the liability to D in a parent on the liability to D in his offspring. Otherwise, all abbreviations are as in figure 1.

TABLE 3. Predicted Risk for the Disorder in Relatives of Affected Individuals Given Varying Degrees of Direct and Indirect Vertical Cultural Transmission of Psychiatric Illness

Path Coefficients[a]			Risk (%)			
			Parents or		Uncles or	Grandparents or
a	b	f	Offspring	Siblings	Nephews	Grandchildren
0.0	0.0	+0.3	5.6	3.0	1.4	1.8
0.0	0.0	+0.5	12.9	12.9	4.4	4.4
0.0	0.0	+0.6	18.8	28.8	9.9	7.3
+0.3	+0.3	0.0	1.4	3.0	1.4	1.1
+0.3	+0.3	+0.1	2.7	3.8	1.7	1.3
+0.3	+0.3	+0.2	4.6	5.8	2.2	1.6
+0.3	+0.3	+0.3	7.5	10.2	3.3	2.3
+0.3	+0.5	0.0	2.6	12.9	2.6	1.4
+0.3	+0.5	+0.1	4.6	17.7	3.7	1.6
+0.3	+0.5	+0.2	7.6	28.4	5.9	2.2
+0.3	+0.5	+0.3	12.1	55.4	10.7	3.4

[a]See table 1 for definition of path coefficients.

TABLE 4. Fitting Models of Vertical Cultural Transmission to Results From M. Bleuler's Swiss Family Studies of Schizophrenia (23)

	Observed		Predicted Under Three Models of Vertical Cultural Transmission					
			Direct and Indirect		Indirect Only		Direct Only	
Relationship	Risk	Correlation in L(D)[a]	Risk	Correlation in L(D)[a]	Risk	Correlation in L(D)[a]	Risk	Correlation in L(D)[a]
Offspring	9.6	0.43	9.0	0.41	4.0	0.23	10.6	0.45
Siblings	9.3	0.42	9.3	0.42	9.0	0.41	9.0	0.41
Nieces and nephews	2.3	0.13	2.4	0.14	4.0	0.23	3.0	0.18
Grandchildren	3.8	0.22	4.0	0.23	2.3	0.13	3.4	0.20
Fit of model[b]								
χ^2			0.13		14.67		1.76	
df			1		2		3	
p			0.71		0.001		0.62	

[a]L(D)=liability to the disorder.
[b]By chi-square goodness of fit test.

fers considerably from that predicted by our earlier models of indirect vertical cultural transmission. Only when the regression of liability to the disorder in offspring on liability to the disorder in their parents is very high (e.g., f>0.5) will the pattern of risk of illness (siblings> offspring>nephews>grandchildren) more closely resemble that produced by indirect vertical cultural transmission. Even under these circumstances, which predict a magnitude of familial aggregation rarely seen in a psychiatric disorder, the pattern differs from that seen in the models for indirect transmission by predicting higher risks in offspring than in nephews.

Including all three sources of familial resemblance for liability to the disorder in the model (figure 3) produces expected correlations for liability to the disorder in relatives that are relatively complex and difficult to interpret (table 1, fifth line). Therefore, we turn to predictions of the risk of illness in relatives (table 3).

When the magnitude of indirect cultural transmission is considerably greater than that for direct transmission (e.g., b>>f), the pattern of illness differs little from that predicted by the second model (table 3). The main effect is that the risk of illness is slightly greater in offspring than in nephews. When the magnitudes of indirect and direct cultural transmission are comparable, then the risk of illness in offspring considerably exceeds that found in nephews. However, even under these circumstances, the risk for illness is greater in siblings than in offspring and greater in nephews than in grandchildren. *When both indirect and direct vertical cultural transmission for the liability to the disorder are present, the pattern of risks of illness in relatives resembles that found with indirect transmission alone unless the magnitude of direct transmission approaches that of indirect transmission. Even when the direct and indirect paths are of equal magnitude, certain features of the observed pattern of risks in relatives (e.g., higher risks in siblings versus offspring) continue to resemble that found in previous models of indirect transmission.*

AN APPLICATION OF THE MODELS TO OBSERVED DATA

Until now, these models for cultural transmission have been used to simulate data. It is important to note that methods are available to determine which, if any, of these models can explain "real" data. The studies chosen for this illustrative analysis, performed by M. Bleuler in Switzerland (23), provide estimates of risk for definite schizophrenia in the following relatives of schizophrenic individuals: siblings, 83/891=9.3%; offspring, 10/104=9.6%; nieces and nephews, 13/ 556= 2.3%; and grandchildren, 1/27=3.8%.

Details of this analysis are provided in appendix 1 and table 4. The first model (indirect transmission for the liability to schizophrenia only) failed badly because relatives other than siblings demonstrated risks for the illness greater than that expected in the population (results not shown). The second model (indirect transmission for the liability to schizophrenia plus direct vertical cultural transmission for predisposing traits) also failed to explain the data. This occurred because the pattern of risk in relatives predicted by this model (siblings>offspring=nephews>grandchildren) was very different from that observed by Bleuler (offspring> siblings>>grandchildren>nephews). The addition of a spousal correlation for the liability to schizophrenogenic traits (the third model) still could not provide a good explanation of the observed data. The fourth model (direct plus indirect vertical cultural transmission for the liability to schizophrenia) provided a very good fit to the observed data. It could be shown, however, that this fit was entirely the result of direct and not indirect transmission of the liability to schizophrenia. That is, a model with only direct vertical cultural transmission for the liability to schizophrenia also provided an excellent fit to the observed results. *Applying these four models to one large family study of schizophrenia produces results inconsistent with the hypothesis that indirect vertical cultural transmission,*

as defined in these models, plays an important role in the familial transmission of schizophrenia.

DISCUSSION

This paper began by noting that most of the literature on the nongenetic transmission of psychiatric disorders within families advocates a model of indirect vertical cultural transmission. I have therefore outlined and examined the predictions of a series of models incorporating this form of familial transmission. Each of the models was bivariate, including both a liability to the disorder and a postulated set of parental predisposing traits.

The paper has three major goals: 1) to illustrate the pattern of risk for psychiatric illness in first- and second-degree relatives of affected individuals, as predicted by specific models for the cultural transmission of the liability to psychiatric illness; 2) to show that these models could be applied to real data by model-fitting methods; and 3) to illustrate a process for the articulation of rigorous and testable models for the nongenetic transmission of psychiatric disorders.

Specific Predictions

A model incorporating only indirect vertical cultural transmission for liability to the disorder produces a highly unrealistic pattern of risks of illness in relatives, under which only siblings have a risk in excess of population expectation. The addition of direct vertical cultural transmission for the liability to predisposing traits produces a more realistic and distinct pattern of risks. Specifically, risks for the disorder, in this model, will always follow the pattern: siblings>offspring (or parents)=nephews (or uncles)>grandchildren (or grandparents).

The addition of a spousal correlation for the liability to predisposing traits produces no change in the overall pattern of risks in relatives. Finally, the addition of direct vertical cultural transmission for liability to the disorder produces only modest changes when the magnitude of the direct transmission is less than that of the indirect transmission. For example, the risk of illness in offspring becomes greater than that in nephews, although it always remains less than that found in siblings. If the contribution of direct vertical cultural transmission for liability to the disorder is assumed to be as great as or greater than that of indirect transmission, then the predicted pattern of risks in relatives, while conserving certain features of the pattern, deviates significantly from that found with previous models.

The pattern of risk for the disorder in relatives predicted by indirect cultural transmission derives from a fundamental feature of these models: siblings will always share liability to illness through having been exposed to the same parental predisposing traits. By contrast, liability to illness in parents can only be transmitted to offspring by a circuitous, two-step process whereby liability to illness in parents is correlated with parental levels of the predisposing trait, which in turn influences liability to illness in children. Because siblings are always more highly correlated for liability than are parent-offspring pairs, uncle-nephew pairs will always be more highly correlated than grandparent-grandchild pairs. This occurs because nephews are offspring of siblings, while grandchildren are offspring of offspring.

Model Fitting

A method was illustrated for testing the fit of the models of cultural transmission to real data. The pattern of risk for schizophrenia observed by M. Bleuler in the relatives of schizophrenic patients (23) could not be accounted for by indirect vertical cultural transmission of the liability to schizophrenia. By contrast, the findings could be well explained by direct vertical cultural transmission. Since I did not formally test models of genetic transmission, and the predictions for genetic and direct vertical cultural transmission can be similar, these results should not be interpreted as strong evidence for direct vertical cultural transmission of schizophrenia. In fact, others have fit path models for genetic and direct cultural transmission for schizophrenia to this and other family data on schizophrenia and have concluded that the familial aggregation of this disorder is largely due to genetic factors (25).

These results do suggest that indirect vertical cultural transmission, as operationalized in these models, does not appear to play a major role in the familial transmission of schizophrenia. Pooled results from family studies of schizophrenia are also consistent with this conclusion (26), since the pattern of risks in relatives (children>siblings>>grandchildren>nephews) is very different from that predicted by models which include indirect vertical cultural transmission.

Are there any psychiatric disorders in which the pattern of risk of illness in relatives of affected individuals resembles that predicted by the second and third models? Such a pattern is not found for affective illness (e.g., 27, 28), alcoholism (e.g., 29) or anxiety disorders (e.g., 30, 31). These results raise the question of whether parental predisposing traits play as important an etiologic role in psychiatric disorders as is often postulated.

However, these kinds of studies are not optimal for testing the models outlined in this paper, since they contain no information on the distribution of predisposing traits in relatives. Wynne and associates (32) examined a quantitative index of psychopathology and a putative predisposing trait (communication deviance) in 114 probands, 44 of whom had schizophrenia, and in both of their parents. In a preliminary analysis that applied the models and methods illustrated in this paper (Kendler et al., unpublished

results), there was evidence for 1) spousal correlations for both communication deviance and psychopathology, 2) direct cultural transmission for communication deviance, and 3) both direct and indirect cultural transmission for psychopathology. While far from definitive, these results demonstrate that indirect vertical cultural transmission for the liability to certain psychiatric disorders may be important and that the models outlined here are sufficiently powerful and flexible to detect its presence.

The Development of Testable Models for Cultural Transmission

The early literature on the environmental transmission of psychiatric disorders within families was largely descriptive (e.g., 1–5). Recently, investigators have developed experimental tests of their hypotheses (e.g., 6, 8–10, 32–34). While such work represents a critical advance in this field, the absence of clearly articulated models for the nongenetic transmission of psychiatric illness remains an important limitation.

Our understanding of the role of genetic factors in the etiology of psychiatric illness has been greatly facilitated by the elucidation of the mechanisms of genetic transmission. This knowledge has been used to generate clear, testable hypotheses about the predicted pattern of risk of illness in various classes of relatives.

It should be possible to articulate models for cultural transmission which, although more complex, approach the precision of that for genetic transmission. Such models can serve at least three critical functions. First, they can provide a priori predictions that can then be empirically tested. Second, the models can indicate what kinds of relationships are most informative for study. Third, they can clarify the mechanism of cultural transmission of the liability to psychiatric illness.

Potential Limitations

A tension exists in all model building between the need for simplicity and the complexity of reality. Because the goal of this paper was heuristic, the models that were outlined here may err on the side of simplicity. Five limitations of these models are particularly worthy of emphasis.

First, the models do not include genetic transmission of the liability to psychiatric illness. Incorporating genes into a complete model would also require consideration of genetic influences on the development of predisposing traits and possible interactive effects between genetic and cultural transmission on the liability to psychiatric illness. For example, genes may in part act by making an individual more or less sensitive to the pathogenic aspects of his rearing environment (35). For disorders influenced by genetic factors, the predictions of these models would still be easily tested in adoption designs. For example, indirect vertical cultural transmission would predict 1) an increased risk of illness in adoptive or step-siblings of affected individuals and 2) a risk in these step-siblings in excess of that found in adopted offspring of ill adoptive parents.

Second, I did not consider a model in which predisposing traits and liability to the disorder were inherently correlated. One plausible way to model this would be to assume a direct effect of liability to the disorder on predisposing traits (e.g., being depressed would make a parent overprotective). The correlations and expected risks for such a model are available from the author on request. In brief, modest effects of liability to the disorder on predisposing traits produce only a small perturbation in the expected pattern of risks of illness in relatives. However, the results of large effects of liability to the disorder on predisposing traits begin to resemble the pattern seen with direct cultural transmission of liability to the disorder. This occurs because liability to the disorder in parents, by influencing the parental level of predisposing traits, can now more "directly" affect liability to the disorder in offspring.

Third, the models assume that the psychological effect of one parent on offspring is additive to the effect of the other parent. This may be unrealistic. For example, some theories of the psychological etiology of schizophrenia emphasize the pathogenic potential of a specific combination of parental characteristics (e.g., an aggressively overinvolved mother plus a distant, ineffectual father), rather than the schizophrenogenic features of a single parent. Such interactions are not adequately captured by the model that incorporates spousal correlations for predisposing traits.

Fourth, the predisposing traits in the model are assumed to be enduring parental characteristics that would equally affect all members of a sibship. These kinds of parental traits can be relatively easily measured. However, a parent's behavior might be pathogenic only for a certain offspring. For example, one member of a sibship could be "chosen" by a parent for special attention because of early behavioral abnormalities. This "special" parent-child relationship might then markedly influence vulnerability to psychiatric illness in that offspring only.

Fifth, these models have made a number of assumptions about "direction of effect." For example, we assume that the correlation between predisposing traits in a parent and psychiatric illness in an offspring results from the impact of a parent on his child. However, a parent could develop what might be labeled "predisposing" traits as a reaction to the manifestations of psychiatric illness in his offspring.

To capture many of the subtle aspects of familial interactions that govern liability to psychiatric illness, it may be necessary to introduce time into these models. Progress has been made in the articulation of rigorous developmental models (36, 37), and their application to psychiatric problems may prove revealing.

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APPENDIX 1. Results of Model Fitting

The first step in the model fitting was to convert the risk figures for definite schizophrenia in relatives that were given by Bleuler (23) into correlations of liability by using an estimated population risk for schizophrenia of 1.0% (table 4). The next step was to fit a series of specific models for cultural transmission to the correlations in liability and their standard errors. This required computer optimization, performed using weighted least squares by routine EO4JAF from the National Algorithms Group (24). The degree to which the models accurately describe the observed results was assessed by a chi-square goodness of fit test, while the relative fit of different models was measured by an approximate likelihood ratio chi-square test. With only information on the risk for the disorder in relatives, the estimates for certain of the path coefficients in some of the models are highly correlated.

After showing that the model with indirect transmission only (e.g., one path—*b*) failed badly, I fit a model with three paths (i.e., *a*, *b*, and *f*; figure 3), which permits both direct and indirect vertical cultural transmission for the liability to schizophrenia. This model fit the data well ($\chi^2=0.13$, df=1, p=0.71). To determine whether this good fit required both direct and indirect cultural transmission, I then fit the second model (i.e., paths *a* and *b*; figure 2), which permits only indirect vertical cultural transmission for the liability to schizophrenia. The deterioration in fit was highly significant ($\chi^2=14.5$, df=1, p=0.0001) and was due to the requirement in this model for the risks to be equal in offspring and nephews and greater in nephews than in grandchildren (table 4). Next, I fit a model with only direct vertical cultural transmission (i.e., path *f* only). No significant deterioration in fit was seen ($\chi^2=1.7$, df=2, p=0.57), since the predicted risks were quite close to those observed (table 4). The estimate of *f* was 0.451.

Adding Bleuler's results on the risk for schizophrenia in spouses (1.7%, with a correlation in liability equal to 0.08) permits the test of the basic model with a path for spousal correlations for the liability to schizophrenogenic traits. This model (i.e., paths *a*, *b*, and *d*) also fits poorly ($\chi^2=14.7$, df=1, p<0.0001).

Drugs and the DST: Need for a Reappraisal

Robert P. Kraus, M.D., Paul Grof, M.D., and Gregory M. Brown, M.D.

It has generally been assumed that psychotropic drugs do not influence results on the dexamethasone suppression test (DST), except in some specific situations. Yet they directly affect the activity of many neurotransmitter systems, which in turn regulate hypothalamic-pituitary-adrenal (HPA) axis functioning. Several reports have shown correlations between the intake of or recent withdrawal from psychoactive substances and changes in DST results. A review of the DST literature reveals that these effects have not been controlled in most DST studies. It is therefore possible that the consequences of intake of psychotropic agents may have contributed to the debate surrounding the DST by producing unappreciated spurious DST results.

(Am J Psychiatry 1988; 145:666–674)

The functioning of the hypothalamic-pituitary-adrenal (HPA) axis and its relationship to psychiatric illness has long been of interest. In the past decade this interest has been stimulated by the standardization of a test of the feedback regulation of the HPA axis (1)—the single-dose overnight dexamethasone suppression test (DST) (2). The utility of the DST has become a subject of considerable debate (3–5), in part reflecting the conflicting data that have appeared in different reports of DST studies. This discrepant DST literature was recently reviewed by Arana et al. (5).

In the past few years, more emphasis has been placed on studies designed to assess potential confounding variables affecting the DST than on studies of DST sensitivity and specificity (5). One potential source of DST variability involves the effects of psychotropic compounds in tested subjects. In earlier large-scale DST studies (2, 6), the question of potential drug effects was assessed by retrospectively comparing similar groups of patients with diagnoses such as depression, who were or were not receiving psychotropic medications, and looking for differences in rates of DST nonsuppression. Few differences were found, and it was concluded that drug use, except in specific instances (such as drugs potentiating dexamethasone metabolism), did not influence DST results, aside from the changes drugs might produce in the subjects' clinical condition (2). In 1981 Carroll et al. (2) published a list of exclusionary medical criteria (including the use of a number of drugs) that could invalidate the DST. Since then most studies have controlled for only the variables included in this list, so that DST results (especially nonsuppression) have been interpreted as correlating with diagnosis, clinical state changes, and so on. Potential confounding effects of psychotropic compounds consumed before or during the times of study have generally not been considered as contributing to the results.

Recent evidence, however, challenges the assumption that drugs lack direct effects on the DST. In fact, some psychoactive substances may commonly and potently influence DST results. For example, single doses of caffeine (equivalent to four or five cups of coffee) can produce nonsuppression in a majority of control and psychiatric subjects (7). Withdrawal from antidepressants frequently results in transient DST nonsuppression (8), and subjects with anxiety disorder who recently discontinued regular benzodiazepine use were found to have twice the rate of positive DST results of similar patients who had not recently discontinued benzodiazepine use (9). Finally, in a prospective study using extensive psychotropic drug screening at the time of admission (10), transient DST nonsuppression occurred in all subjects who had discontinued one or more of a variety of psychotropic compounds (including antidepressants, benzodiazepines, and neuroleptics). Much of the previous drug use was indicated only on the drug screening and not on detailed drug histories. Despite these accumulating data, most researchers and clinicians continue to assume a lack of direct effects of drugs on the DST, as indicated by the paucity of attempts to control for such factors, even in very recent DST studies.

The early assumption that drugs do not influence the DST appears counterintuitive. The known neurotransmitter regulation of corticotropin-releasing factor (CRF) secretion, for example, would strongly suggest the potential of psychotropic drugs to influence HPA axis

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function and thus DST results, given the established effects of these compounds on the same neurotransmitters that regulate CRF. The recently documented drug effects on the DST are therefore not surprising and might have been predicted from knowledge of CRF regulation.

In this paper we will examine the question of drug effects on the DST. We will summarize the literature on the neurotransmitter regulation of CRF and then the effects of different psychotropic agents on these neurotransmitter systems, illustrating the potential for these compounds to influence cortisol output. The complete regulation of glucocorticoid secretion is not completely understood (11), and as new knowledge accumulates other avenues may emerge by which medications could be predicted to affect the DST. We will then move to pharmacological and clinical data. The available studies reporting medication effects on the HPA axis in general and the DST in particular will then be presented. Finally, we will evaluate DST and HPA axis studies in the psychiatric literature, assessing what measures were included in the methodologies of these studies to exclude potential medication effects. Our conclusion is that some of the conflicting DST literature may reflect the confounding effects of psychotropic and other compounds, producing possibly invalid study results.

NEUROTRANSMITTER REGULATION OF HPA ACTIVITY

There is considerable evidence that certain neurotransmitters tend to stimulate and that others tend to inhibit CRF secretion. Neurotransmitters that stimulate CRF secretion include acetylcholine (through both nicotinic and muscarinic receptor actions), serotonin, histamine (through H_1 receptors), and compounds with β-adrenergic agonist activity. In contrast, α_2-adrenergic, γ-aminobutyric acid (GABA), enkephalin, angiotensin II agonists, and melatonin, along with glucocorticoids, inhibit CRF activity. Vasopressin acts in synergy with CRF to increase ACTH secretion and is thus considered a "stimulating" neurotransmitter.

As reviewed by Hillhouse et al. (12), acetylcholine stimulates basal CRF release in the rat by actions on both nicotinic and muscarinic receptors (13, 14). Physostigmine, which raises acetylcholine activity, can raise cortisol levels enough to overcome cortisol suppression after dexamethasone administration in man (15, 16), an effect that can be blocked by pretreatment with atropine (15). Whether the physostigmine effects on the DST are due to peripheral (17) or central (18) mechanisms is unclear.

Serotonin also stimulates CRF release, leading to increased glucocorticosteroid secretion in vivo in man (19). This is true regardless of whether the increased serotonergic system activity is induced by precursor loading, by a serotonin uptake inhibitor, by serotonin releasers, or by direct-acting serotonin agonists (20).

Histamine, through H_1 receptors, has an excitatory central effect on CRF secretion and results in adrenal secretion in both dogs (21) and man (22).

Studies of the effect of adrenergic stimulation on CRF secretion are conflicting, reflecting the several classes of receptors stimulated by noradrenaline. Some studies suggest, however, that β-adrenergic receptors stimulate ACTH release and that dexamethasone normally suppresses isoproterenol-induced increases in ACTH (23).

In contrast to β-adrenergic stimulation of CRF secretion, α-adrenergic receptor agonists, such as clonidine, inhibit the secretory activity of the HPA axis, at least when administered acutely (24, 25).

Opioids are thought to inhibit HPA axis activity (26–29), possibly acting at a suprapituitary site (28). Naloxone produces the opposite effect to that of opioids: elevation of cortisol levels (29). Actual responses to opioids in psychiatric subjects might depend very much, however, on the functioning of the HPA axes in individual subjects before exposure to opioids, as illustrated by the lack of effect of naloxone on serum ACTH levels in some patients with Cushing's disease (30).

As reviewed by Jones et al. (31), GABA inhibits CRF secretion and may play an inhibitory role in the stress response. The implications of GABA-mediated inhibition of CRF secretion are important in considering the possible effects of benzodiazepines on the DST.

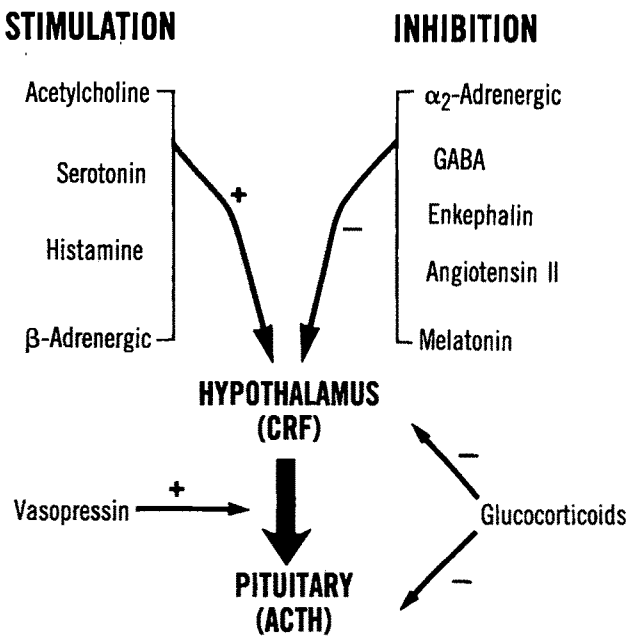
Melatonin, a possible marker for adrenergic function (32), may act to inhibit the HPA axis, but any cause/effect relationship between reduction of melatonin and elevation of cortisol levels (33) is difficult to identify in view of the mutual regulating effects of each of these hormones on the other (33).

There is little evidence for any direct physiologic role of dopamine in CRF or HPA axis regulation (12, 13). The inhibitory effects of dopamine agonists, such as L-dopa on CRF secretion (34), are thought to be mediated by inhibitory noradrenergic mechanisms rather than by dopaminergic actions (24). Although some direct inhibitory role for dopamine has been suggested by some investigators (35), studies of this question are complicated by the fact that increases in free dopamine can be induced by dexamethasone (36).

Endogenous and exogenous glucocorticoids directly inhibit both CRF and ACTH secretion (1). This negative feedback is a complex phenomenon. Dexamethasone, a synthetic glucocorticoid, acts similarly to cortisol in normally suppressing cortisol secretion for 24–36 hours by means of a "slow feedback" mechanism (1), and this action forms the basis of the "normal suppressor" pattern on the DST (2).

Vasopressin is thought to act synergistically with CRF, amplifying CRF-stimulated ACTH release and synthesis (37). A pituitary vasopressin receptor may undergo down-regulation when exposed to chronically high levels of hypothalamic vasopressin (as is the case following adrenalectomy) (38), suggesting that a sim-

FIGURE 1. Neurotransmitter Regulation of CRF and ACTH Secretion



ilar phenomenon may occur in other neurotransmitter systems under conditions of chronic stimulation.

The influences of the neurotransmitters noted here and other factors on CRF activity are summarized schematically in figure 1. It should be emphasized that most of this work has been done with single-bolus stimulation tests of the neurotransmitter systems (the DST tests the suppressibility of the HPA axis, not its excitability) and that the HPA axes being tested were, for the most part, in animals and not in humans. There are pronounced differences in the regulation of HPA axis secretion in different mammalian species (1), and effects during chronic exposure may be quite different from those following acute neurotransmitter stimulation or inhibition. Therefore, this summary should not imply that this information can be used to predict with certainty the effects on the DST of influencing the activity of these neurotransmitter systems. This is especially true for psychotropic compounds because they may influence multiple neurotransmitter systems directly and indirectly.

DRUG EFFECTS ON NEUROTRANSMITTER SYSTEMS

A detailed review of the effects of psychotropic compounds on neurotransmitters is beyond the scope of this paper, but we will summarize the neurotransmitter effects of the major classes of medications.

Tricyclic antidepressants potentiate the actions of catecholamines to varying extents by blocking neuronal reuptake. They also have antimuscarinic, antihistaminic (H_1), and peripheral α-adrenergic blocking actions, and over time they induce postsynaptic β-receptor subsensitivity (39, 40). The monoamine oxidase inhibitors (MAOIs), by inhibiting catecholamine degradation, produce initial increases in the concentrations of biogenic amines (39), but after 2 to 3 weeks inhibition of catecholamine, neurotransmission may develop (41). MAOIs and the newer antidepressants bupropion, trazodone, and nomifensine have little effect on acetylcholine neurotransmission (39, 42).

Lithium has multiple effects on neurotransmitter system activities, and contradictory reports make it difficult to summarize the relevant literature (43). Lithium tends to lower noradrenaline and dopamine neurotransmission but augments serotonergic activity and tends to normalize abnormal acetylcholine muscarinic activity. Acute lithium withdrawal produces rebound increases in the activity of noradrenergic (44), serotonergic (45), and cholinergic systems that may persist for several weeks (45).

All neuroleptics seem to have in common the ability to block dopamine neurotransmission, but they also have varying degrees of anticholinergic, antihistaminic, antiserotonergic, and antiadrenergic actions (39). Antimuscarinics are often used to treat neuroleptic-induced motor side effects, with the exception of amantadine, which is a dopamine agonist (39).

Benzodiazepines appear to exert no effects on the neurotransmitters histamine, serotonin, acetylcholine, or adrenaline (46). Their therapeutic actions are thought to be due to an enhancement of presynaptic inhibition by interacting with GABA and binding to benzodiazepine receptors (47). Buspirone, a nonbenzodiazepine anxiolytic, does not bind to benzodiazepine receptors and has a mixture of dopamine agonistic, serotonin agonistic, and α-adrenergic antagonistic activities (47).

Other compounds, not often considered "drugs," have important neurotransmitter system effects (39). Caffeine antagonizes the neuromodulator adenosine, which has been shown to inhibit release of acetylcholine, dopamine, norepinephrine, serotonin, and GABA (48). Nicotine causes catecholamine release as well as stimulation of acetylcholine-nicotinic receptors. Alcohol produces elevations in catecholamine concentrations, alters their central distribution (especially that of serotonin), and markedly stimulates opioid receptor transmission.

OTHER MECHANISMS FOR CONFOUNDING DST RESULTS

Although changes in CRF "drive" due to neurotransmitter system effects may be one route by which drugs could confound DST results, other mechanisms are possible. Drugs could influence the assay procedures used in DST studies—for example, by inducing changes in concentrations of cortisol binding proteins. Changes in dexamethasone concentrations could occur due to drug influences on dexamethasone absorption or metabolism, resulting in very low or very high

dexamethasone levels leading to false-positive or false-negative DST results, respectively. For example, many anticonvulsants are known to produce false-positive DST results by means of increased hepatic metabolism of dexamethasone (2, 49), although additional mechanisms may be involved in specific instances. The measurement of plasma dexamethasone (50) can help identify cases in which spurious DST results are due to unusual dexamethasone concentrations. A review by Lowy and Meltzer (51) details factors, including drugs, that can influence dexamethasone bioavailability.

STUDIES OF DRUG EFFECTS ON HPA AXIS ACTIVITY

We will now review studies of the actual effects of drugs and other compounds on measured secretion patterns of hormones arising from the HPA axis, concentrating on studies of psychotropic drugs.

The effects of acute administration of antidepressants on DST results are different from those observed during regular intake. Single intravenous doses of tricyclic antidepressants stimulate plasma cortisol secretion (52), although patients with endogenous depression tend to show blunted cortisol increases compared with control subjects (53). However, subjects with HPA axis abnormalities may respond differently to tricyclic antidepressants. Patients with Addison's disease show no CRF or ACTH secretion response to intravenous desipramine; in fact, intravenous desipramine has a paradoxical effect on feedback mechanisms in these patients: the normally negative feedback effects of a glucocorticoid infusion are converted to positive effects, resulting in pronounced transient increases in plasma cortisol (54).

Longer-term tricyclic antidepressant treatment studies usually reveal no increases in basal or DST plasma cortisol levels compared with pretreatment values (55). In a single patient receiving 1000 mg/day of desipramine for several years, no abnormalities of cortisol levels or diurnal rhythm were noted during continued intake or during or after slow tapered withdrawal (56). In another report (57), consistent normalization of DST nonsuppression in a patient with depression and dementia was observed during repeated courses of treatment with three tricyclic antidepressants; there was some resolution of vegetative signs but not of dementia.

Together, these reports indicate that single doses of tricyclic antidepressants may produce transient basal cortisol elevations, possibly enough to overcome cortisol suppression after dexamethasone administration, but that regular tricyclic antidepressant treatment usually has no substantial effects on the DST, although false normalization may occur occasionally. The differential effects of acute and chronic tricyclic antidepressant administration are in keeping with the neurotransmitter changes that are produced by tricyclic antidepressants over time (58).

Although slow tapered withdrawal may be unlikely to affect the DST (54), abrupt discontinuation of antidepressants may regularly produce transient HPA activation and conversion of normal DST results to nonsuppression for periods of up to 3 weeks (8, 10). The discontinued drugs that have produced transiently positive DST results in these studies have included imipramine, desipramine, amitriptyline, trimipramine, nortriptyline, maprotiline, doxepin, and alprazolam.

Since regular antidepressant treatment produces β-adrenergic receptor down-regulation, presumably because of chronically increased β-adrenergic activity, and β-adrenergic agonists acutely stimulate CRF secretion, it is likely that the "unmasking" of increased β-adrenergic activity after abrupt cessation of antidepressants is at least partly responsible for the resulting increases in HPA axis output.

We could not find any studies of potential direct DST effects of MAOIs. A study of the effects of different psychoactive substances on the circadian rhythm of urinary glucocorticoid excretion in rats (59) showed a distinct phase delay in the peak of secretory activity in animals treated with pargyline in doses that drastically inhibit both type A and type B monoamine oxidase activity. The results of this study suggest a need for further investigations of the effects of MAOIs on the DST.

As for the anticholinergics, atropine in single doses can block acetylcholine-induced DST nonsuppression in man (15) and can block the expected morning circadian cortisol increase in cats (60), but the effects of repeated doses of anticholinergics (used, for example, to manage drug-induced parkinsonism) are unclear (61). We are not aware of any studies of the effects of anticholinergic withdrawal alone—not as part of antidepressant withdrawal—on the DST.

Acute chlorpromazine administration, similar to acute antidepressant treatment, stimulates basal HPA axis secretion (62), and this effect may continue for the first 2–3 weeks of continuous treatment (63). However, treatment longer than 4–6 weeks tends to inhibit the levels of HPA axis hormones (62). As with antidepressants, abrupt withdrawal of neuroleptics has been reported to produce marked increases in basal plasma cortisol levels (64) and transient DST nonsuppression (10, 65).

Benzodiazepines can falsely normalize the DST when taken in doses exceeding 20 mg/day of diazepam or the equivalent (2, 66). Not as well appreciated is that even routine doses of benzodiazepines such as oxazepam may acutely lower basal cortisol levels (67) and that routine doses of benzodiazepine hypnotics (loprazolam and triazolam) can reduce cortisol levels when used regularly. Rebound cortisol hypersecretion then occurs during withdrawal (68). Such findings are compatible with the GABA-enhancing effects of benzodiazepines. We recently reported the development of positive DST results 3–7 days after abrupt cessation of benzodiazepines and lasting at least 3 weeks in individual cases (10), but we have not observed any such

changes in serial DST results in patients undergoing slow tapered benzodiazepine withdrawal from chronic high doses (unpublished observations). Whether short-term or occasional benzodiazepine use can produce positive DST results after discontinuation (as might occur in studies using a "drug-free" interval) is an important question for future research to answer given the common practice of prescribing benzodiazepines "as needed" in psychiatric patients.

Estrogen compounds can produce DST nonsuppression in normal women (69), but this does not reflect any increase in plasma free cortisol. Although low-dose estrogen treatment (e.g., in oral contraceptives) usually does not have this effect (2), false-positive DST results may be observed in occasional subjects taking birth control pills (70).

Anticonvulsant drugs (phenobarbitone, phenytoin, and primidone) that stimulate hepatic enzymes interfere with dexamethasone metabolism and produce false-positive DST results (49). However, sodium valproate, which reportedly does not accelerate dexamethasone metabolism or stimulate hepatic enzymes, also commonly produces positive DST results (49), so that additional mechanisms may be responsible. Carbamazepine, of use in rapid-cycling bipolar patients (71), also raises baseline cortisol levels and can produce DST nonsuppression (72), but the exact mechanisms are unclear.

In the only report that we are aware of concerning over-the-counter medications, Rush et al. (73) found positive DST results in more than half of a group of normal adults taking different prescription drugs (nasal decongestants, sympathomimetics, contraceptives, thyroid hormones) or suffering from untreated upper respiratory infections, venereal disease, or allergies.

We indicated earlier in this paper that no clear role for dopamine in the physiological regulation of CRF secretion has emerged. However, in hypercortisolemic states, dopamine agonists have been repeatedly found to acutely inhibit HPA axis activity (74). These effects are virtually the opposite of those observed for acute neuroleptic administration (62), as might be expected.

Acute lithium treatment causes a transient (less than 24 hours) increase in basal corticosteroid levels (39). We are not aware of systematic DST studies on the effects of lithium, but the prominent neurotransmitter system effects of regular lithium intake and abrupt withdrawal suggest at least the potential for influencing DST results. Any DST studies with lithium should include methods that acknowledge the marked differences in effects that lithium may produce in different groups of subjects. This may be especially true for the neuroendocrine effects of lithium. One study (75) showed that lithium treatment produces marked differences in the patterns of neuroendocrine responses to insulin-induced hypoglycemia compared with pretreatment responses in the same subjects, depending on whether the subjects were normal control subjects, bipolar patients who responded well to lithium, or bipolar patients who responded poorly to lithium. By inference, a lack of DST effects for any substance should not be taken for granted if this conclusion is based solely on studies showing a lack of DST effects in normal control subjects or in patients significantly different from the index group to be investigated. Clinically disparate groups may show quite different neuroendocrine test patterns when given the same medication.

Regular lithium or MAOI treatment can augment tryptophan-induced increases in serum cortisol (76), implicating serotonergic-mediated CRF stimulation for these compounds when they are taken regularly.

Acute alcohol intake produces transient increases in the levels of HPA axis hormones (39), but whether such increases could overcome suppression by dexamethasone is unknown. In contrast, chronic high-dose alcohol intake seems not to influence HPA axis secretion (77). Withdrawal from chronic alcohol intake, which has been widely studied, regularly produces positive DST results for at least 3 weeks after cessation of drinking in a majority of subjects (78–81).

An unresolved issue is whether abrupt cessation of moderate or social alcohol use (such as would occur in many psychiatric subjects and normal control subjects beginning a DST study in the hospital) might also produce false-positive DST results (10).

Tobacco, coffee, tea, and cola beverages are often not considered psychotropic medications when drug histories are taken for DST studies. We are not aware of any studies of the effects of nicotine in any form on the DST. Caffeine has been studied: it raises basal plasma cortisol levels in both control and psychiatric subjects (82) and, when taken in single doses equivalent to 4–5 cups of coffee, can produce false-positive DST results (7). Certainly many psychiatric patients ingest large amounts of caffeine, and these findings raise the possibility that in some patients with nonsuppression, the DST results reflect caffeine consumption alone rather than the patients' illnesses (7).

In summary, the available literature suggests that acute treatment with antidepressants, neuroleptics, or lithium stimulates HPA axis secretion, possibly enough to overcome cortisol suppression after dexamethasone administration in certain subjects. Regular intake of tricyclic antidepressants, neuroleptics, or alcohol inhibits the HPA axis and may produce occasional DST false normalization. Anticonvulsants, carbamazepine, and estrogens commonly produce positive DST results, and oral contraceptives, cold medicines, and minor illnesses may do the same in some subjects.

Abrupt discontinuation of antidepressants, lithium, neuroleptics, benzodiazepines, or alcohol frequently produces DST nonsuppression lasting for at least 3 weeks after withdrawal. Withdrawal of narcotics, anticholinergics, antihistamines, MAOIs, and sympathomimetics might be predicted to produce the same phenomenon. Acute or chronic use of narcotics, analgesics, benzodiazepines, antihistamines, dopamine agonists, and serotonin antagonists may inhibit the

HPA axis and produce false-negative DST results in certain cases.

Nicotine may eventually be found to stimulate the HPA axis, but studies are not yet available. Caffeine stimulates cortisol secretion, and it may produce nonsuppression in normal and psychiatric subjects.

Thus, many medications not usually considered to influence the DST have been shown to have the potential to directly affect the test. These drug effects are consistent with the known regulation of CRF secretion and the known neurotransmitter effects of these compounds. It is probable that many more substances will be shown to affect the DST in future studies.

POTENTIAL CONFOUNDING DRUG EFFECTS IN DST STUDIES

Using this information, we sought to evaluate the methodologies of published DST studies with respect to the strategies that were used to avoid the possibility that the actions of medications and other psychoactive substances might have confounded the results.

We reviewed all studies included in a published compilation of the DST literature through 1983 (83) as well as studies included in major reviews of the DST (*5*, *65*). For each study we noted 1) the diagnostic groups in the study, 2) results of DSTs in the subject groups, 3) whether subjects were drug free at the time of DSTs and, if so, for how long, 4) whether the report specified medications and doses being taken by subjects during the study period, 5) whether drug screening was performed to validate the drug-free condition or compliance with prescribed medications, and 6) whether strategies were used to determine intake or any cessation of intake of medicines in the 2 months before the DST was administered.

Our review included all available studies of the "diagnostic utility" of the DST for melancholia and major depression as well as studies investigating the DST in depression as a predictor of specific treatment response, risk of relapse, or suicide risk. Some studies used several methods in addition to the DST to characterize HPA axis functioning, including 24-hour profiling of plasma ACTH and/or cortisol rhythms before and/or after dexamethasone administration and evaluation of the relationship, if any, between ACTH levels and DST results. Since some direct drug effects might be more evident on these non-DST measures than on the DST itself, we evaluated the study methods in these latter reports in the same way we evaluated the DST studies. Most of these non-DST studies indicated that subjects "remained on their usual psychotropic medications" during the period of testing.

Almost all of the DST studies mentioned adhering to the exclusionary criteria (including medications) listed by Carroll et al. (2). Some of the more recent reports also excluded subjects taking carbamazepine or oral contraceptives. The usual method of referring to potential drug effects was a statement such as, "No subject was taking medications known to influence the DST," with a reference to Carroll et al. (2).

With few exceptions, reports did not list medications being administered to subjects at the time of DST administration. Because this potentially relevant information was not presented, the validity of the DST findings and the resulting conclusions in most reports could not be reevaluated in the light of more recently identified confounding medication factors.

Even in the studies that identified drugs being taken at the time of DST administration, doses and duration of treatments were usually omitted. No study indicated any method of validating compliance with prescribed treatments, such as quantitative serum levels or qualitative urinary drug screening. Similarly, no study used any objective method of ensuring that drug-free patients were truly without exposure to drugs for the prescribed intervals (10). This acceptance of patients' self-reporting of recent medication intake is contrary to the extensive literature attesting to the problems with ensuring compliance and the unreliability of drug histories in psychiatric patients (10, 84–86).

Only one study, by Coryell et al. (9), mentioned attempts to determine medication discontinuations (aside from alcohol) by subjects in the few weeks immediately preceding DST administration. This failure to indicate recent drug cessations was true for all the studies in which a drug-free interval was used before the DST was given. With the exception of only two of the drug-free studies, in which DSTs were administered no earlier than 4 weeks after the last medication intake (87, 88), the drug-free period in these studies was 7–14 days. It will be recalled that the studies of drug withdrawal effects have consistently shown that withdrawal produces nonsuppression for at least *3 weeks* (8–10). Thus, the studies with a 1–2-week drug-free interval may have inadvertently included some nonsuppression results that reflected the cessation of psychotropic agents at the start of the drug-free intervals. Paradoxically, this source of spurious nonsuppression might be less prevalent in studies that did not use a drug-free interval.

No study mentioned or indicated attempts to document amounts of caffeine being consumed by subjects. Although the possibility that caffeine intake might produce false-positive DST results is a general concern in all DST studies (7), the specifics of certain studies make it imperative to control for the HPA activating effects of caffeine. For example, studies of the DST in relation to sleep deprivation (89) might be quite likely to yield false-positive results if subjects were allowed to drink unlimited amounts of coffee in order to keep themselves awake during the deprivation nights.

SUMMARY AND COMMENT

This review indicates that psychotropic compounds have potential for confounding DST results. Neuro-

transmitter systems regulate the secretory activity of the HPA axis by regulating CRF secretion, and psychotropic agents profoundly influence these same neurotransmitter systems. Drug-induced effects on neurotransmitter systems are not static over time, and the results on CRF secretion change as the timing of medication intake varies from acute to chronic exposure and to cessation of exposure (withdrawal). These facts, along with the reality that most psychotropic drugs affect multiple neurotransmitter systems, make it difficult to reliably predict the actual effects of these compounds on the DST in the absence of systematic studies. Other mechanisms by which drugs could affect the DST include influences on dexamethasone bioavailability.

Given these potential mechanisms, it is not surprising that a growing number of reports document the direct effects of drugs on the DST. For many compounds the effects of acute drug administration on DST results are more pronounced than those observed during chronic use, although the direct effects of regular use may still influence DST results in individual subjects. However, the abrupt discontinuation of drugs that tend to inhibit cortisol secretion may be of greatest importance because such withdrawal might lead to pronounced HPA activation and produce positive DST results for 3 or more weeks in a majority of subjects. This phenomenon can occur in the absence of withdrawal symptoms.

These drug effects might be observed to a greater or lesser extent in as-yet-undefined subgroups of patients. As a further potential variable, unexpected paradoxical responses to medications can occur, especially in subjects with preexisting abnormalities of HPA axis functioning at the time of drug exposure or withdrawal.

Our evaluation of the methodologies and findings in the DST literature suggests that the potential influence of drugs on the DST has been underestimated by many researchers. However, the extent to which drug effects might have confounded results in DST studies is impossible to determine. The reporting in the studies that we evaluated was almost always incomplete in the aspects of medication use at the time of DST administration, recent medication discontinuation, validation of compliance, and validation of the drug-free condition. The generally incomplete drug documentation might also reflect inconsistent study methodologies with respect to potential confounding drug effects that may have resulted in spurious DST results in some cases. A combination of inconsistent methodologies and spurious results could have contributed to the controversy surrounding the DST itself by producing conflicting findings in the DST literature.

There appears to be a need for a reappraisal of the question of drug effects on the DST. Many compounds may turn out to be innocuous as far as DST results are concerned, but drugs with actions on neurotransmitter systems should be strongly suspected of having effects on the DST, at least until systematic studies of the consequences of intake and withdrawal of these substances have been performed. Because drugs may be most likely to affect the DST during either the acute phase of intake or in the period after withdrawal, studies should be designed to investigate potential drug effects within these time periods, and because drug actions may vary depending on the subjects being studied, it may be necessary to repeat these studies with different groups of psychiatric subjects before any conclusions about a particular drug can be made.

Until such work has been completed, we suggest that attempts be made to minimize exposure to psychotropic drugs in subjects in DST studies and that close attention be paid in drug histories to recently discontinued medications. All drugs being consumed by subjects should be reported in DST study publications. In addition, caffeine consumption should be minimized and documented, and the amount of cigarette smoking should at least be monitored. Drug level monitoring for prescribed medications and drug screening to validate drug-free intervals might be necessary in certain studies to ensure that reporting of drug intake has been accurate (10).

The DST has great potential value in research and clinical psychiatry, but this potential can be realized only if confounding factors (5) are systematically identified and controlled to ensure valid test results. Unknown drug effects may have contributed to the current state of confusion about the DST. We hope that future research will clarify these effects and permit a more valid assessment of the clinical utility of the DST.

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Polydipsia and Hyponatremia in Psychiatric Patients

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Many psychiatric patients have polydipsia and polyuria without identifiable underlying medical causes. Hyponatremia develops in some polydipsic patients and can progress to water intoxication with such symptoms as confusion, lethargy, psychosis, and seizures or death. This syndrome is sometimes called "compulsive water drinking," "psychogenic polydipsia," and "self-induced water intoxication." Although the underlying pathophysiology of the syndrome is unclear, several factors have been implicated in producing polydipsia and symptomatic hyponatremia. These include a possible hypothalamic defect, the syndrome of inappropriate secretion of ADH (SIADH), and neuroleptic medication. Evaluation of psychiatric patients with polydipsia includes a search for other medical causes of polydipsia, polyuria, hyponatremia, and SIADH. Treatment modalities currently available include fluid restriction and medications.

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In 1938 Barahal (1) described a case "in which a female dementia praecox patient drank excessive quantities of tap water resulting in edema, coma, convulsions, with subsequent recovery." Since that time we have learned that many psychiatric patients drink excessive quantities of water and that some of these patients develop symptoms of water intoxication. It has become equally clear, however, that not all patients with water intoxication recover uneventfully. Water intoxication carries a substantial risk of morbidity and mortality and may become a recurring problem. The recognition and proper management of patients with this problem are therefore important aspects of psychiatric care.

Earlier papers (2, 3) have provided brief overviews of the problems of polydipsia and hyponatremia in psychiatric patients. In this paper we will review these topics in more detail, elaborating the relevant pathophysiology and presenting a comprehensive approach to evaluation and treatment.

The terms used to identify and classify psychiatric patients who have polydipsia and polyuria with and without accompanying hyponatremia have not been well-defined or consistently applied (3). Descriptive terms used have included "compulsive water drinking" (4), "self-induced water intoxication" (5, 6), "self-induced water intoxication and psychosis" (7), "psychogenic polydipsia," "primary polydipsia," and the "psychosis-intermittent hyponatremia-polydipsia (PIP) syndrome" (3). Some of these terms imply elements that are not necessarily involved, such as willfulness, psychological drive, or compulsion. It may be more accurate to limit the labels used to the simple, descriptive terms: "polydipsia" and "hyponatremia" in psychiatric patients.

HISTORICAL PERSPECTIVE

In the early 1930s investigations seeking a physiologic basis for schizophrenia were undertaken. Hoskins and Sleeper (8, 9) did extensive physiologic testing on a large sample of inpatients at Worcester State Hospital in Massachusetts. Their results were remarkable for the difference in urine volumes in schizophrenic patients compared with normal control subjects. Not only did schizophrenic patients excrete an average urine volume twice that of normal control subjects, but they also showed a larger than normal variation in their pattern of excretion. The etiology of the polyuria was unclear, but Sleeper (10) subsequently performed water load and water deprivation tests and was able to demonstrate that the polyuria resolved with control of polydipsia and that diabetes insipidus was not present.

Over the next several decades little attention was paid to polydipsia and polyuria in psychiatric patients until 1958, when Barlow and DeWardener (4) described the clinical features of compulsive water drinking and noted a history of psychological disturbance in eight of their nine polydipsic patients. The syndrome of inappropriate secretion of ADH (SIADH) was described by Schwartz et al. (11) in 1957, and in 1963 Hobson and English (6) identified SIADH in a schizophrenic patient with compulsive water drinking. Since that time recognition of polydipsia and water intoxication in psychiatric patients has grown, and it is becoming clear that these are common problems.

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EPIDEMIOLOGY AND CLINICAL PHENOMENOLOGY

Epidemiologic studies indicate that the prevalence of polydipsia ranges from 6% to 17% of chronically ill psychiatric patients (12–14). It is believed that one-quarter to one-half of psychiatric patients with polydipsia will go on to have symptoms of water intoxication (12, 13). Among psychiatric patients with polydipsia, schizophrenia is by far the most frequent diagnosis, being found in 69%–83% of these patients (11, 14–17). Polydipsia has also been associated with affective disorders, mental retardation, alcoholism, postencephalitic disorders, organic brain syndrome, anorexia nervosa, and personality disorders. Polydipsia can occur in patients without identifiable medical or psychiatric illness (14, 15, 18–28).

The prevalence of polydipsia and water intoxication may be slightly higher in women; in several series (4, 12, 16, 29), 60%–80% of the patients were female. Jose and Evenson (16) noted a high incidence of previous ECT administration in their symptomatic hyponatremic patients. Caution must be exercised regarding interpretation of prevalence data because it is not always possible to obtain a history of excessive water drinking. Smith and Clark (30) were able to elicit a history of excessive water intake from the patients or the family of only 50% of their patients with episodes of water intoxication. Gleadhill et al. (29), however, found that 80% of his patients were observed to drink excessive amounts of water.

It is unclear how specific signs and symptoms of psychiatric illness relate to polydipsia. In 1936 Sleeper and Jellinek (31) compared schizophrenic men whose urine output was high with those whose urine output was low. They found that the men with high urine output had higher IQs, less emotional deterioration, more affective symptoms, and a slightly higher incidence of paranoia. There was no difference between the two groups in the age at onset of illness, however. Nearly 50 years later, Lawson et al. (32) confirmed that early work. They also found that the urine volume of schizophrenic patients was about twice that of the normal population and noted a higher frequency of polydipsia and polyuria in schizophrenic patients with good premorbid histories and good responses to neuroleptics. In addition, all three patients with documented hyponatremia had tardive dyskinesia and two had ventricle enlargement, neither of which was present in four patients with polyuria but no hyponatremia.

Kirch et al. (17) identified eight schizophrenic patients with chronic hyponatremia who had in common a high incidence of poor response to neuroleptics and a diagnosis of chronic undifferentiated subtype. The mean age at illness onset of these patients was 20.7 years, and three of the patients had persistent tardive dyskinesia. There was evidence of intellectual decline in three of the four patients whose intelligence was tested and lateral ventricle enlargement on CT scan in four of the six patients whose brains were scanned. Increased third ventricle size and early lateral ventricle enlargement were also seen in the pneumoencephalographic study of a single schizophrenic patient with polydipsia and hyponatremia (33). This clinical description coincides with that of "type II" schizophrenia proposed by Crow (34). Crow described type II schizophrenia as characterized by a chronic course, poor response to neuroleptics, intellectual impairment, and a relatively high frequency of tardive dyskinesia and CT scan abnormalities. Although the number of patients studied is too small to draw definitive conclusions, it could be postulated that the subgroup of polydipsic patients who develop hyponatremia might include those with more evidence of neurologic impairment.

Vieweg et al. (35, 36) emphasized the progressive nature of water and electrolyte abnormalities in the schizophrenic population. Taking the patients' life histories as a whole, they found that polydipsia with or without polyuria and hyposthenuria develops 5–15 years after the onset of psychiatric illness. In those patients who develop water intoxication, the symptoms tend to appear another 1–10 years after the onset of polydipsia. Jose and Evenson (16) reported a mean interval of about 19 years (range=11–36 years) between the onset of psychosis and the first symptoms of water intoxication.

Vieweg et al. (3) placed the onset of water drinking in the "preterminal" stage of schizophrenia. As described by Arieti in 1945 (37), this stage "occurs 5–15 years after disease onset, characterized by disorganization, lack of emotional content, and compulsive behavior."

CLINICAL PRESENTATION

Patients with polydipsia usually come to medical attention in one of three ways: water seeking and water drinking are noted by the patient or observers, hyponatremia or hyposthenuria is found incidentally in laboratory testing, or medical intervention is required for symptoms of overt water intoxication.

Water drinking and water seeking may or may not be subtle, and the patient may make an effort to hide it. Noonan and Ananth (22) reported on a patient in whom "excessive water drinking had been well concealed . . . and not suspected by the staff . . . . She was found to lie in the bathtub with her mouth to the faucet in such a way that the sound of running water could not be heard." In some cases, the patient may be unaware that his or her fluid intake is excessive. Even when not hyponatremic, these polydipsic patients often demonstrate polyuria, dramatic weight fluctuations, and/or incontinence and are often found on laboratory evaluation to have a low urine specific gravity and a low BUN (31, 35, 36).

The signs and symptoms of water intoxication were first described by Rowntree in 1923 (38) and are es-

sentially those of hyponatremic encephalopathy: headache, blurred vision, weakness, muscle tremor and cramps, nausea and vomiting, diarrhea, excessive salivation, restlessness, confusion, lethargy, psychosis, seizures, coma, and death (39). Headache, blurred vision, generalized malaise, nausea, and vomiting occur early. Diarrhea and increased salivation may be noted, and hyperpyrexia and anhidrosis have been reported (6). Mental status changes are often seen, especially confusion, restlessness, irritability, and lethargy. Some patients may show psychotic or manic symptoms (40, 41). It may be difficult clinically to differentiate an exacerbation of psychosis from early signs of hyponatremic encephalopathy, and a check of the serum sodium level may be necessary when there is a change in the behavior of a polydipsic patient (40). Since the serum sodium level can drop rapidly over the course of a day, it may be necessary to recheck the level whenever the patient's clinical status changes (42). Seizures and coma may supervene or be the initial presentation of water intoxication and are more likely to occur if the drop in sodium level is severe or precipitous (15, 39, 43). There may be a fatal outcome (23, 44–46). Death in water-intoxicated patients is usually attributed to pulmonary or cerebral edema (23, 44, 47, 48). Vieweg et al. (46), reviewing the causes of mortality in schizophrenic patients, found that as many as 18% of the deaths of schizophrenic patients under 53 years of age may be related to water intoxication.

In addition to the acute effects already described, polydipsia and polyuria can produce chronic illness. Long-term complications include bowel and bladder dilation. The latter may progress to hydronephrosis and renal failure (35, 49–51). Congestive heart failure is also a possible complication.

The key factor in the CNS effect of hyponatremia remains uncertain. Dodge et al. (47) noted that the symptoms are probably secondary to hypo-osmolarity of the serum rather than hyponatremia, since the administration of mannitol to water-intoxicated animals results in improvement of the clinical and EEG signs of encephalopathy while the serum sodium concentration is still below normal. In the clinical setting, however, in the absence of severe hyperglycemia, hyperlipidemia, or uremia, the serum sodium level is the major determinant of serum osmolarity (39).

PATHOPHYSIOLOGY

Explanations of the pathophysiology of polydipsia and hyponatremia in psychiatric patients need to account for three main aspects of this syndrome: why some patients drink excessive amounts, why only some patients with polydipsia become symptomatically hyponatremic, and why the hyponatremia occurs only episodically in some patients with continuous polydipsia.

Mechanisms of Polydipsia

Under unusual circumstances excessive water drinking appears to be completely voluntary. Emery (52) described alcoholic patients who consumed large quantities of fluids in order to get drunk. Swanson and Iseri (53) reported the case of a patient who became encephalopathic following the ingestion of large amounts of water and use of enemas to relieve constipation. Silber (26) described a patient with anorexia nervosa who drank a large amount of water in order to gain weight quickly before being examined by her physician. Among psychotic patients, the most common explanations offered by individuals who appear to be voluntarily drinking excessive amounts involve purification (to cleanse or purify [30, 54, 55] or to "flush out worms" [56], for example) or other delusional explanations, such as "to prepare for being sucked into the sun" (57).

Some observers cited the anticholinergic effects of many psychoactive medications as a possible exacerbating factor in overdrinking, especially noting the dry mouth such medications can cause (33, 58, 59). Although having a dry mouth may exacerbate drinking in an individual, polydipsia was described before the use of medications and is seen in patients who are not taking medications (1, 4, 8, 24, 45, 55). In addition, treatment with artificial saliva appears to have no impact on water drinking (14). It therefore seems unlikely that dry mouth is a major contributing factor. It has also been proposed that neuroleptics may directly stimulate hypothalamic thirst centers (58). However, well-documented cases of compulsive water drinking in the preneuroleptic era make it clear that medications cannot be the sole cause.

It may be that polydipsia in psychotic patients shares the same underlying pathophysiology as psychosis. There have been repeated observations of patients with polydipsia who increase their fluid intake at times of psychotic exacerbation and whose water drinking and laboratory findings become more normal as the psychosis remits (27, 55, 60, 61). It is unclear, however, how closely the increased water intake and psychotic exacerbation parallel each other. Mandell et al. (60) gave patients water load tests and the MMPI. They found an improvement in "psychological dysfunction" that paralleled improved clearance of free water. Shen and Sata (62) noted a number of episodes of water intoxication among polydipsic patients when their neuroleptic doses were decreased. The water drinking became more normal and the severity of psychosis decreased when the dose of neuroleptic was raised. Lawson et al. (32) reported that scores on the Brief Psychiatric Rating Scale reflecting the severity of illness roughly paralleled the patients' urine output. Dubovsky et al. (55) noted a decrease in water intake and reversal of SIADH when psychiatric symptoms improved; water intake increased and SIADH returned when psychosis recurred. Hobson and English (6) also noted a temporal relation between psychosis and psy-

chogenic polydipsia. Raskind et al. (61), however, noted the resolution of hyponatremia and SIADH during an episode of psychotic exacerbation without any improvement in psychotic symptoms in one patient, and Vieweg et al. (63) found no significant correlation between Mini-Mental State Examination scores and serum sodium levels. Thus, the question remains open as to how closely the course of psychosis parallels that of polydipsia and hyponatremia.

The hypothalamus is the area of the brain most closely linked to fluid and electrolyte balance. The proposed location for the internal osmostat that controls serum osmolarity is the lamina terminalis at the anterior border of the third ventricle (64). Drinking behavior appears to be mediated largely by the lateral hypothalamus. The supra-optic nucleus of the hypothalamus, also located anterior to the third ventricle, is the site of synthesis for ADH, also known as vasopressin. In 1963 Hobson and English (6) proposed that self-induced water intoxication may be a disorder of hypothalamic control. Sklar and Schrier (64) pointed out that the supra-optic nucleus also projects to the cortex, amygdala, and brainstem and could therefore play a role in psychiatric disease as well as electrolyte balance.

Given the finding of an increased prevalence of ventricle enlargement in schizophrenic patients with polydipsia and hyponatremia, one might postulate a structural defect in the hypothalamus (which surrounds the third ventricle) as either accounting for or being caused by ventricle enlargement and leading to a hypothalamic functional deficit in thirst and electrolyte balance, as Peterson and Marshall (33) proposed in their patient with polydipsia, SIADH, and hydrocephalus.

Dopamine appears to be important in the control of thirst and drinking and may be a common link between psychosis and polydipsia. As already noted, thirst and drinking are mediated or facilitated by the lateral hypothalamus, and dopamine is an important neurotransmitter or neuroregulator in this region. In animals, electrolytic lesions of the lateral hypothalamus result in adipsia and aphagia. A similar picture is seen following injection of 6-OH dopamine into the nigrostriatal dopamine pathway, and this decrease in fluid intake is reversible by dopamine agonists. Injection of dopamine into the lateral ventricles or of apomorphine into the hypothalamus can initiate drinking. Injection of the dopaminergic antagonist haloperidol into the lateral hypothalamus or septal area blocks drinking secondary to water deprivation (65, 66). Thus, it appears in animal experiments that a hyperdopaminergic state is associated with increased fluid intake and dopamine depletion is associated with decreased fluid intake. This would be consistent with a hyperdopaminergic hypothesis for the etiology of polydipsia similar to the dopamine hypothesis of schizophrenia and the dopamine supersensitivity hypothesis of tardive dyskinesia (30, 61, 62, 67). Lawson et al. (32) found a higher incidence of tardive dyskinesia in schizophrenic patients with hyponatremia and polyuria than in control schizophrenic patients. Shen and Sata (62) noted that two patients experienced transient tardive dyskinesia when their compulsive water drinking was exacerbated, supporting the idea that dopamine supersensitivity underlies both these conditions.

Other theories have been advanced proposing links between polydipsia, hyponatremia, psychosis, and ADH. One theory is that ADH itself may be a neuroregulator of norepinephrine, dopamine, and/or endorphins. Thus, the increase in ADH levels seen in some patients could be viewed as an attempt to restore "the homeostasis of disturbed norepinephrine and dopamine systems" (24). Another theory is that since ADH has known effects on learning, memory, and behavior, disordered ADH may be directly involved in the abnormalities seen in psychiatric disease (46). Yet another theory posits that opiate agonist binding may be more effective in the presence of a lower sodium level and that patients with polydipsia may, by drinking, increase endogenous opiate receptor effects by decreasing the concentration of sodium in the cerebral environment (46). In contrast to this concept, Robertson et al. (68) noted that opiates increase the threshold to ADH release and may increase the threshold for thirst.

Mechanisms of Hyponatremia

It remains unclear why only a subgroup of patients with polydipsia become hyponatremic. The episodic nature of hyponatremia in these patients has led to a search for factors that might influence when a patient with polydipsia progresses to frank water intoxication. It is important to note that hyponatremia does not usually develop from simply drinking too much water, since the renal capacity for free water excretion (about 28 liters/day) is usually more than adequate to handle large fluid volume loads (39, 55, 69). It is well documented and generally accepted that, with rare exceptions, water intoxication develops only when high fluid intake is coupled with one or more factors compromising the excretion of free water.

There have been rare case reports of extremely high fluid intake overwhelming the kidneys and producing water intoxication (69, 70). Nielsen (70) reported on a drug-free patient with water intoxication caused by increased oral intake and enemas who had normal renal function and whose laboratory values were not consistent with impaired water excretion at the time of treatment. Most patients, however, demonstrate impairment of free water excretion; the syndrome of SIADH is an especially common finding.

SIADH. Under normal physiologic circumstances hyponatremia elicits an endocrine response that leads to the conservation of sodium and the excretion of free water. In a 1957 report, Schwartz et al. (11) noted that some hyponatremic patients, instead of conserving sodium, continued to lose it in the urine as if under the influence of ADH at a time when ADH release should

have been suppressed. Bartter and Schwartz (71) called this the syndrome of inappropriate secretion of ADH.

The current criteria for diagnosing SIADH are hyponatremia and hypo-osmolarity of the serum and extracellular fluid with continued renal excretion of sodium. These factors result in an osmolarity of the urine greater than that appropriate for the tonicity of the serum (i.e., the urine is less than maximally dilute). SIADH can be diagnosed only in the presence of normal renal, cardiac, and adrenal function and the absence of fluid volume depletion.

Hobson and English (6) were the first to note SIADH in psychiatric patients with polydipsia. Many have since indirectly identified SIADH by means of water load testing and urine and serum electrolyte measurements. More recently it has become possible to confirm high levels of circulating ADH by radioimmunoassay. Several psychiatric patients with polydipsia have now been shown to have elevated levels of arginine vasopressin during episodes of water intoxication (35, 36, 61).

SIADH may have many causes. A variety of tumors secrete ectopic ADH (such as carcinoma of the lung, duodenum, or pancreas). A number of neurologic conditions also lead to ADH secretion (possibly secondary to hypothalamic dysfunction). These include encephalitis, hemorrhage, stroke, tumor, trauma, and Guillain-Barré syndrome. Pulmonary disorders, such as pneumonia, tuberculosis, and pulmonary abscess, may lead to SIADH. Medications associated with SIADH include the hypoglycemic drugs chlorpropamide and tolbutamide and the antineoplastic drugs vincristine and cyclophosphamide. Clofibrate, acetaminophen, and thiazide diuretics are also associated with SIADH (72, 73).

Many factors may play a role in eliciting ADH release in psychiatric patients with polydipsia. Stress has been shown to stimulate ADH release, and there are those who feel that an acute psychotic exacerbation may have the same nonspecific effect (6, 55, 74). Others doubt that stress plays a substantial role in ADH release (61, 64). The possibility raised by Fowler et al. (74) that SIADH may be due to hyponatremic seizures is unlikely, since many psychiatric patients with SIADH have not had convulsions.

Many drugs can cause SIADH and thereby impair renal excretion of free water. Those drugs with particular importance to psychiatry include carbamazepine, thioridazine, amitriptyline, desipramine, tranylcypromine, thiothixene, fluphenazine, haloperidol, chlorpromazine, and nicotine. Moses and Miller (72) reviewed the evidence for implicating different drugs as causing SIADH. Sandifer (73) focused on psychoactive drugs with a reported association to SIADH and found that in half of the instances the implicated drug had been used for less than 1 week. The importance of careful measurement of urine and serum electrolytes and osmolarity and the utility of drug rechallenge to document the relationship between any medication and SIADH have been emphasized by researchers in this area. Medication-related SIADH is usually reversible when the drug is discontinued. Even SIADH that seems clearly drug related (i.e., it resolves when the drug is stopped and recurs with drug rechallenge) may be temporally limited, and it may be possible to give the same drug again in the future without recurrence of SIADH (73, 75). Drugs can cause SIADH and water intoxication in the absence of polydipsia (20, 26).

Nicotine is a potent stimulator of ADH release (64, 76, 77). Jose and Evenson (16) found that 69% of their patients with self-induced water intoxication were smokers. Blum (77) noted in his study of patients with compulsive water drinking that symptomatic hyponatremia developed only in those who were heavy smokers. Blum (77) and Chin et al. (78) reported on patients with polydipsia who developed SIADH and water intoxication only when smoking. These authors found normal water load test results in the absence of nicotine but abnormal results suggesting SIADH when the patients were permitted to smoke.

Diuretics. Diuretics are a major exacerbating factor in the hyponatremia experienced by many patients. Diuretics interfere with sodium resorption at the proximal tubule, exacerbate sodium excretion, impair free water excretion, and may lead to acute water intoxication (19, 79, 80). Jose et al. (15) felt that water intoxication may have been related to diuretic use in 12% of the patients they studied. Smith and Clark (30) felt that diuretics were such a major factor in the development of hyponatremia that they classified their patients with water intoxication into three groups: "pure water drinkers" (i.e., those with unexplained etiology), patients with SIADH, and patients taking diuretics. The presence of diuretics makes it more difficult to maintain electrolyte balance, and their use should be avoided.

"Reset osmostat." Linquette et al. (81) proposed that patients with polydipsia and hyponatremia might have a lowered threshold for ADH release. This was documented by Hariprasad et al. (82), who reported on a group of patients with low serum sodium levels who did not initially appear to have SIADH because their urines were also diluted. However, during fluid deprivation tests, the urine became concentrated while the serum remained hypo-osmolar. They termed this phenomenon "reset osmostat" and postulated that it might be a protective response to chronic hyponatremia in some patients which functions to dampen swings in electrolyte levels at the expense of perpetuating hyponatremia. Although some authors believe that a reset osmostat is distinct from SIADH and may be confused with it if the urine-diluting capacity is not examined when the plasma is very dilute (82, 83), others have stated that it is a variant of SIADH (84).

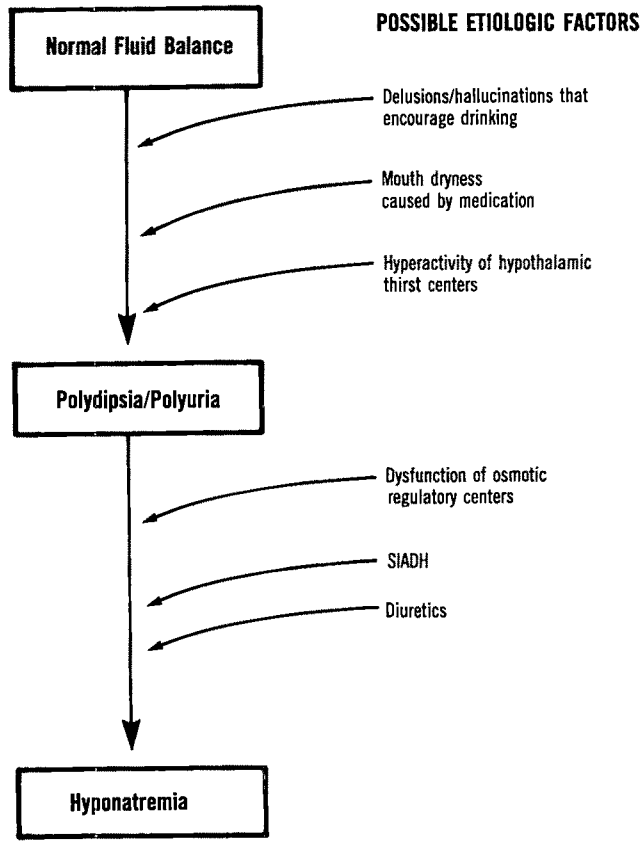
Renal involvement. It is possible that the kidney itself influences the development of hyponatremia and a hypo-osmolar state. Researchers (49, 85, 86) have found that high fluid intake decreases renal concentrat-

ing ability to some extent in normal volunteers. It is possible that the kidney might respond to chronic fluid loading by developing a supersensitivity to normal or low levels of ADH, causing fluid retention and hypo-osmolarity. However, this is not supported by the studies cited (35, 36, 61), which document elevated ADH levels by radioimmunoassay in this patient population.

A General Pathophysiologic Scheme

The results of different studies on the epidemiology and pathophysiology of polydipsia and hyponatremia can be summarized as follows. It appears there is an underlying abnormality in some psychiatric patients, perhaps related to the pathophysiology of their psychiatric disease, that results in their developing polydipsia at some point in the course of their illness. The polydipsia is indicated by polyuria and low urine specific gravity. Other factors contributing to excess fluid intake may include delusional beliefs or medication side effects. At some time after developing polydipsia, the patient's fluid dynamics change: he or she retains free water and/or excretes excessive amounts of sodium, which in turn may lead to hyponatremia and the syndrome of water intoxication. Contributing factors in the development of hyponatremia may be a resetting of the hypothalamic osmostat or the inappropriate release of ADH due to stress, psychosis, nicotine, or medication (see figure 1).

FIGURE 1. Evolution of Polydipsia and Hyponatremia in Schizophrenic Patients



EVALUATION AND TREATMENT

The management of psychiatric patients with polydipsia has several aspects: 1) identifying the patient as a water drinker and ruling out other causes of polydipsia, polyuria, or hyponatremia, 2) determining if SIADH is present, 3) management of acute hyponatremia, and 4) long-term management and prophylaxis.

Identification of the Patient

The initial evaluation should focus on eliminating other known causes of polydipsia. Polydipsia and polyuria are also seen in diabetes mellitus, diabetes insipidus, chronic renal failure, hypocalcemia, and hypokalemia. They are also found with the use of drugs such as lithium, diuretics, and alcohol. The differential diagnosis of hyponatremia includes pseudohyponatremia (a low serum sodium level in the presence of normal serum osmolarity that usually results from the presence of high amounts of circulating glucose or hyperlipidemia), dehydration with salt depletion, renal dysfunction, heart failure, hepatic failure, and endocrine disorders.

The patient's history should be obtained with special attention to the amount of fluid consumed and excreted, behavior in seeking fluids, and the signs, symptoms, and frequency of hyponatremic episodes. The use of medications and their temporal relation to episodes of polydipsia or polyuria should be noted.

In the physical examination signs of congestive heart failure, organomegaly, edema, dehydration, encephalopathy, or focal neurologic deficit should be sought.

The initial laboratory evaluation should include a CBC, measures of electrolytes, glucose, and serum osmolarity, and liver function tests. Endocrine function can be screened by measuring morning cortisol level and by thyroid function tests. A urinalysis should be obtained with attention to specific gravity, glycosuria, and direct measurement of urine osmolarity and urinary sodium level. An EEG is important in any patient with seizures and can also give useful information in patients with subtle signs of hyponatremic encephalopathy. A CT scan of the head can rule out structural pathology such as a pituitary or hypothalamic tumor. A chest X-ray will screen for lung cancer, a well-known cause of SIADH.

It is usually difficult, if not impossible, to obtain patient cooperation for a complete 24-hour urine collection to evaluate the extent of polyuria. There are methods for obtaining fairly accurate estimates of 24-hour urine volumes based on the measurement of urinary creatinine excretion (87).

Diagnosis of SIADH

The diagnosis of SIADH can be made on the basis of low serum sodium concentration and osmolarity with a relatively concentrated urine. If the presence of SIADH remains uncertain, a water load test, which evaluates how well the kidneys can excrete free water, can be done. In some laboratories ADH can be measured directly by radioimmunoassay. If SIADH is present, other underlying medical causes should be sought before attributing it to psychosis.

Acute Management

Hyponatremic seizures, like other generalized seizures, can be managed with intravenous anticonvulsant medication if required. Some physicians advise correction of the sodium deficit with hypertonic saline. This, however, may not be the best way to manage hyponatremic patients. There is strong animal and clinical evidence (88–90) that the rapid correction of hyponatremia can induce demyelination of the pons and other areas of subcortical white matter. Central pontine myelinolysis can be associated with the development of bulbar palsy, quadriplegia, coma, and death within days of the correction of hyponatremia. It seems prudent, therefore, to treat the seizures separately and use fluid restriction to allow the hyponatremia to gradually and safely resolve whenever possible.

Long-Term Management

The mainstay of management of patients with persistent water drinking remains fluid restriction and the removal of exacerbating factors. If these methods are unsuccessful, medications may be useful. Since there may be an association between the psychotic process and polydipsia, polyuria, and hyponatremia, an attempt must be made to maximally treat the patient's psychiatric disorder. On the other hand, in those cases in which a psychotropic medication appears temporally related to the development of water intoxication, a trial off the medication should be attempted. Diuretics, which can cause renal sodium loss and SIADH, should be discontinued and an alternative antihypertensive substituted. Cigarette smoking should be kept to a minimum in order to decrease exogenous ADH stimulation. Fluid restriction is difficult to enforce but should be tried whenever possible. If it is too difficult to maintain constant fluid restriction it may still be possible to manage inpatients who become hyponatremic intermittently by following body weight once or twice a day. When an abrupt rise in body weight signals an acute increase in fluid intake, the serum sodium level can be checked. If hyponatremia is found, fluid can be temporarily restricted until the acute exacerbation passes (91).

High-dose oral sodium chloride supplementation (6–82 g/day) with or without fluid restriction has been tried with partial success. The usefulness of such supplementation is limited because salt is rapidly lost in the urine, polyuria and hyposthenuria persist, and progressively higher doses of salt are required. There is also a high incidence of hypertension subsequent to this treatment (84). For these reasons, this approach is not recommended.

Shevitz et al. (92) proposed the use of high-dose propranolol based on the findings that isoproterenol (a β-adrenergic agonist) increases thirst in some settings and that propranolol (a β-adrenergic antagonist) is useful at high doses in schizophrenia. He noted successful treatment of both psychosis and water drinking in a patient receiving a dose of propranolol as high as 320 mg/day. The side effects of such doses of propranolol are substantial, and in the absence of controlled trials in patients with polydipsia, polyuria, or hyponatremia, propranolol is not recommended as a first-line approach.

ECT has been recommended for water drinking associated with psychosis (4, 54). Raskind and Christopher (93) reported on a single patient whose psychosis and SIADH resolved following ECT. This is another area in which controlled studies have not been done.

Several medications that affect ADH secretion or its action at the kidney have been tried in patients with SIADH. Although patients whose seizures are clearly secondary to hyponatremia rarely require chronic anticonvulsant treatment, phenytoin has a transient ability to suppress ADH release and may be helpful in some patients (94, 95). Lithium has long been known to produce nephrogenic diabetes insipidus; however, its low therapeutic index and the possible irreversibility of the induced diabetes insipidus make it less than ideal for chronic management of hyponatremia (96, 97). Moreover, in some patients lithium appears to centrally stimulate thirst. A more promising drug for prophylaxis is demeclocycline, an antibiotic related to tetracycline, which can induce a reversible nephrogenic diabetes insipidus and has been used to treat SIADH of other etiologies (97–99). Preliminary reports on the use of demeclocycline in psychiatric patients with polydipsia (100–102) show that it may be beneficial in controlling both hyponatremia and polydipsia even in the absence of classical SIADH.

SUMMARY

Polydipsia and polyuria without identifiable medical cause are found in 6%–17% of psychiatric patients and are especially common among patients with chronic schizophrenia. A hyperdopaminergic state in hypothalamic thirst centers may stimulate increased fluid intake. A subgroup of polydipsic patients develop symptoms of hyponatremia. SIADH is found in many of these patients and in some cases may be related to antipsychotic medication. Fluid restriction is the main management technique used. Demeclocycline, how-

ever, may be more useful in the long-term treatment of these patients.

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Gender Differences in the Course of Schizophrenia

Jill M. Goldstein, Ph.D.

This study tested the hypothesis that schizophrenic women experience a less severe course of illness than schizophrenic men. Ninety patients with DSM-III diagnoses of schizophrenia, who were in the early stages of illness, were followed for 10 years with respect to rehospitalizations and length of time in the hospital. Multivariate regression techniques were used to test for gender differences across multiple outcomes. The women experienced fewer rehospitalizations and shorter stays than did the men. These findings were not an artifact of diagnosis. The results suggest that the determinants of gender differences occur during the premorbid period and are manifest early in the development of the disorder.

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A number of studies have reported differences between schizophrenic men and women with respect to age at onset and at first hospitalization (1–4), symptom expression (5, 6), family history (7), course of illness (8–12), treatment response (2, 13), and biological indices such as structural brain abnormalities (14). However, there has been little systematic investigation of these findings, and much of the literature on schizophrenia still assumes that the illness is similar in men and women. The validity of gender differences in schizophrenia has important consequences for understanding the nature of the illness. That is, if there are significant gender differences in age at onset, expression, family history, biological factors, and course of illness, perhaps what is called "schizophrenia" is expressed as different subtypes in men and women.

This study focused on gender differences in the course of schizophrenia, one of the criteria for diagnostic validity (15). The literature on gender differences in the course of schizophrenia is somewhat variable because of diagnostic inconsistency and differences in selection of cases, length of observation, and operationalizing dimensions of outcome. One of the major reasons for variability across studies in demonstrating the impact of gender on course of illness is that not all of the samples have consisted of first-admission cases. That is, if schizophrenic women experience a less severe course of illness than men do, then a sample with multiple hospitalizations would exclude the women who recover after one episode, thus attenuating the effect of gender on the course of illness.

Of 21 first-admission longitudinal studies from 1960 to the present that were reviewed (e.g., 10, 11, 16, 17), only one showed no significant gender differences for any outcome, although the attrition rate during that study reached 82% (16). Findings from other first-admission studies showed that schizophrenic women experienced fewer rehospitalizations, shorter hospital stays, better social and work functioning, better response to neuroleptics, lower relapse rates, and less severe psychopathological outcomes (10, 11, 17). (A complete list of these studies can be obtained from the author on request.)

In 19 multiple-admission longitudinal studies, the results were more variable. Many of the studies found that schizophrenic women experienced fewer rehospitalizations and shorter hospital stays than schizo-

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phrenic men (8, 9). Only one study found that schizophrenic *men* had lower rehospitalization rates (18), although several found no significant gender differences in rehospitalizations or lengths of hospital stay (4, 19). (An exhaustive review of these studies is provided in a 1987 paper by Angermeyer et al., available from the author on request.)

Findings from the studies reviewed demonstrated that gender differences in the course of schizophrenia were strong enough to arise even when the effect was attenuated by the use of a sample with multiple hospitalizations. However, there have been few studies that have used samples of schizophrenic patients diagnosed according to current systems (3, 4). Critics attribute the significant gender differences found in earlier studies that used *DSM-II* criteria for schizophrenia to diagnostic misclassification (4). Their argument is that in studies of schizophrenia diagnosed according to *DSM-II* criteria, the women who experienced a less severe course would have been given diagnoses of affective disorders if *DSM-III* standards had been used. The implication of this criticism is that if adjustments for diagnostic misclassification were made, there would be no significant differences in the courses of illness of schizophrenic men and women given diagnoses based on *DSM-III* criteria.

This study examined gender differences in schizophrenic patients diagnosed by *DSM-III* criteria who were in the early stages of the disorder and who were followed for 10 years. It was hypothesized that the schizophrenic women would experience a less severe course of illness than the schizophrenic men. Analyses were also conducted to begin to explain the effect of gender on the course of schizophrenia.

METHOD

The data for this study were originally collected from the early to middle 1970s for a study funded by the National Institute of Mental Health ("Symptom Tolerance and Recidivism Study" by Drs. Dolores Kreisman and Virginia Joy). The study was primarily conducted at a private psychiatric teaching hospital in New York City, although a small proportion of the patients came from the state facility associated with this hospital. Consecutively admitted patients were entered into the study during 1972–1973 if they met the following criteria: 1) hospital diagnosis of schizophrenia or acute schizophrenia, according to *DSM-II* criteria, on both admission *and* discharge; 2) hospital stay of less than 6 months; 3) expected to return to live with family of origin or with spouse; 4) no organicity, e.g., mental retardation, epilepsy, or organic brain syndrome; 5) no *primary* drug or alcohol abuse; and 6) age between 18 and 45 years.

For the present study, these patients were rediagnosed according to *DSM-III* criteria. Rediagnoses were made from microfilm of chart records and medical test reports. The records at the hospital provided rich, detailed histories of the patients' lives and the development of their symptoms. The diagnosis of schizoaffective disorder was included because it was of interest as a possible subtype of schizophrenia. (Analyses were conducted with and without the data on schizoaffective patients.) Rediagnoses were conducted by the author and by a psychiatrist/diagnostician who was blind to the study hypotheses. Since the author was not blind to the hypotheses, a reliability study (also reported here) was conducted by two expert diagnosticians in the Biometrics Research Unit at the New York State Psychiatric Institute.

All of the women, a random subsample of the men, and all of the men with a *DSM-II* diagnosis of schizoaffective disorder or latent schizophrenia were rediagnosed. This procedure was followed because, out of a random sample of 25 women and 25 men with diagnoses of schizophrenia according to *DSM-II*, more than one-third of the women had been misclassified, compared to approximately one-tenth of the men. Of the original 199 patients with schizophrenia, acute schizophrenia, or schizoaffective disorder according to *DSM-II* criteria, 169 met the *DSM-III* criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

Eight patients (four men and four women) were randomly selected for the reliability study. Their case charts were duplicated, excluding names, medications, and any other possible references to diagnosis. The information was given to two expert diagnosticians who were blind to the study hypotheses. The unweighted kappa for interrater agreement was 0.80. There was only one disagreement about diagnosis: between schizophrenia (one of the experts' diagnosis) and schizoaffective disorder, depressed type (the author's diagnosis). In fact, the expert noted in her report that she could not rule out schizoaffective disorder, depressed type.

As mentioned previously, in order to examine gender differences in the course of schizophrenia, it is necessary to include first-admission cases. Of the 169 cases in which *DSM-III* criteria were met, 52 were first admissions. Since this sample size was small, patients with one previous hospitalization (N=38) were also included, on the assumption that these patients were also in the early stages of the disorder. Combining these two hospitalization groups was a more conservative test of the major hypothesis of the study, since including the group with one previous hospitalization attenuated the effect of gender on the results. However, combining the two hospitalization groups increased the power of the test of gender differences and increased the generalizability of the results. The advantages of having a larger sample outweighed the disadvantages of possibly attenuating the effect of gender. The resulting sample consisted of 90 patients (32 women and 58 men). Analyses comparing the two hospitalization groups on sociodemographic characteristics showed no significant differences.

The sample was young (mean±SD age=24.6±6.2

years), primarily never married (83%, N=75), with a high level of education (mean±SD years completed= 13.3±2.0). The majority were a non-Hispanic white (97%, N=87), middle-class group; approximately 19% (N=17) were in so-called white-collar jobs, 18% (N=16) were in blue-collar jobs, 24% (N=22) were students, 8% (N=7) were housewives, and 31% (N=28) were unemployed in the 6 months preceding their initial hospitalization. The patients were given diagnoses of schizophrenia, paranoid (37%, N=33), schizophrenia, nonparanoid (37%, N=33), schizophreniform disorder (14%, N=13), and schizoaffective disorder, depressed or manic type (12%, N=11).

There were no significant differences between the men and the women in terms of age, education, marital status, religion, and socioeconomic status. Not surprisingly, there were more men than women in blue-collar jobs ($\chi^2=5.91$, df=1, $p<0.02$), and there were more unemployed men than unemployed women. The women usually had white-collar jobs—mostly clerical and sales—or were housewives. In addition, the men had significantly poorer premorbid histories, as measured by Gittelman-Klein and Klein's instrument (20) (mean± SD score for men, 2.84±0.99; for women, 2.24±0.96; t=2.84, df=88, $p<0.01$); significantly more women received schizophreniform and schizoaffective, depressed type, diagnoses ($\chi^2=13.7$, df=4, $p<0.01$), although the sample sizes were small.

Symptoms were rated by trained master's-level interviewers using an instrument developed specifically for the original study. Symptoms included hallucinations, formal thought disorder, paranoia, grandiosity, inappropriate affect and behavior, isolation, withdrawal, anxiety, depressive mood, somatic complaints, dependency, impulsivity, inability to function, obsessive thoughts and behavior, and agitation.

As mentioned, premorbid functioning was assessed by means of the instrument developed by Gittelman-Klein and Klein (20). Isolation, peer relationships, and interests were rated on a 6-point scale for each patient's preadolescence (ages 6–13 years) and adolescence (14–20 years). Overall ratings, consisting of the average of scores across areas (20), were provided in this data set. Other indicators of functioning included marital status (recoded as never married versus ever married) and occupational status (recoded as white-collar or blue-collar job versus unemployed).

In this study, the course of illness was operationally measured by the number of hospitalizations and the length of hospital stays. Hospitalization is a frequently used measure in psychiatric studies. It is a complex outcome, since it indicates severity of illness, clinical treatment, and/or selection into treatment. Data on the course of hospitalizations were obtained over a 10-year period ending in 1983. Data on number of hospitalizations were obtained from the statistical office in the New York State Department of Mental Health. At the time of this study, all private and state hospitals were required to provide data to the state office on all admissions and discharges.

TABLE 1. Rehospitalizations and Length of Hospital Stay During 5-Year and 10-Year Follow-Up of 58 Male and 32 Female Schizophrenic Patients

Outcome	Mean	SD	Two-tailed t (df=88)[a]	p
Number of rehospitalizations				
0–5 years				
Men	1.40	1.59	3.14	0.0001
Women	0.59	0.84		
0–10 years				
Men	2.24	2.84	2.26	0.03
Women	1.12	1.84		
Length of hospital stay (days)				
0–5 years				
Men	267.41	367.59	2.68	0.009
Women	129.97	96.57		
0–10 years				
Men	417.83	675.65	2.09	0.04
Women	206.81	272.27		

[a]When the F value was significant, the separate variance estimate was used to calculate the t value and its significance.

RESULTS

To examine whether schizophrenic men had a higher mean number of rehospitalizations and longer stays in the hospital over a 10-year period, t tests were used. Table 1 shows that the schizophrenic women had a significantly lower mean number of rehospitalizations and shorter stays in the hospital over the 10-year follow-up period. The effect of gender was even stronger during the first 5 years of observation. When a conservative significance level based on Bonferroni's correction for multiple comparisons was used, the effect of gender remained significant over the 5-year observation period (i.e., $p=0.05\div4=0.01$). The stronger effect at 5 years makes clinical sense, given Bleuler's finding (8) that the severity of a schizophrenic patient's psychosis usually does not deteriorate further beyond the severity 5 years after the first episode.

In order to explain the effect of gender on outcome, the 5-year period was examined, since gender had its strongest effect during the first 5 years and thus the largest variability to be explained. Two hypotheses were tested to explain this effect: 1) gender differences in schizophrenia are due to gender differences in early developmental and social history factors; i.e., schizophrenic men have poorer premorbid histories than schizophrenic women (20), and patients with poor premorbid histories experience worse outcomes than those with good premorbid histories (9); and 2) gender differences in schizophrenia are due to gender differences in diagnostic subtypes; i.e., more women receive diagnoses of schizoaffective disorders, and patients

who express affective syndromes experience a better course than those who do not (21).

Since the predictor variables were the same for rehospitalization and length of hospital stay, the use of data analytic techniques for multiple dependent variables was preferable. This controls for possible type I errors by providing a "protected" F test, the results of which must be significant before one can interpret the importance of the predictors of each single dependent variable. In addition, the multivariate F is a powerful test, and the combination of the dependent variables contributes to the significance of the overall F test value, even when the univariate F test values for each dependent variable do not reach significance by themselves. Multivariate regression was used to predict outcomes and was performed by means of a statistical program developed by Cohen and Nee (22). Rao's F was the multivariate F test used in the study.

Table 2 presents the steps performed in the multivariate regression. Step 1 shows that the effects of gender alone on rehospitalization and length of stay were significant, with women experiencing fewer rehospitalizations and shorter stays. (Previous hospitalization was also controlled in step 1 because there were first- and second-admission patients in the sample.)

Gender was entered first into the regression analysis to assess the magnitude and significance of its effect on outcome, represented as a regression coefficient (*b*). Other variables of interest were then entered into the regression analysis to try to explain the significant effect of gender. If a variable or set of variables contributed to explaining the gender effect, the magnitude and significance of the regression coefficient (*b*) for gender would decrease or disappear.

In step 2, premorbid functioning was entered into the regression to assess how much of the effect of gender on outcome might be accounted for by premorbid functioning. As shown in table 2, the effect size of gender on rehospitalization decreased from $b=-0.30$ to $b=-0.26$ when premorbid functioning was entered. The percent decrease in the regression coefficient for gender from step 1 to step 2 in the analysis can be represented as $[(b_1-b_2)/b_1\times100]$ (5). The drop in the regression coefficient for gender from step 1 to step 2 suggests that premorbid functioning accounted for 13% of the effect of gender on rehospitalization; that is, $(0.30-0.26)/0.30\times100=13\%$. For length of stay, premorbid functioning accounted for only 4.3% of the effect of gender on outcome (i.e., from $b=-0.47$ to $b=-0.45$; see step 1 to step 2).

Social functioning indicators (i.e., marital and occupational status) were of less importance in explaining the effect of gender on rehospitalization, accounting for 4.2% more of the effect than premorbid functioning alone. However, social functioning indicators explained 11.3% more of the effect of gender on length of stay than premorbid functioning alone (from $b=-0.45$ to $b=-0.40$; see step 2 to step 3 in table 2).

In step 4, we tested whether gender differences could be explained by differences in subtypes (i.e., schizophreniform and schizoaffective disorders versus schizophrenia). Symptoms at the time of entry into the hospital were also included in the analysis to better control for initial clinical status. Psychotic symptoms and affective symptoms formed two factors that were entered into the regression equation. (Analysis of symptoms is the topic of another paper [5].)

Step 4 in table 2 presents the effects of clinical status after premorbid history and social functioning indicators were controlled. The effect of gender on rehospitalization decreased from $b=-0.249$ to $b=-0.246$ (both numbers shown as -0.25 in table 2) when clinical status variables were entered. This suggests that clinical status explained only 1.2% more of the effect of gender on 5-year rehospitalization. For length of stay, clinical status explained 4.8% more of the effect of gender on outcome (see step 3 to step 4 in table 2).

DISCUSSION

The results of this study demonstrate that schizophrenic women experienced significantly fewer rehospitalizations and shorter hospital stays over 5- and 10-year periods than did schizophrenic men. The results support past studies of first-admission cases that showed significant gender differences in rehospitalization and length of stay and challenge nonsignificant findings from some past studies in which patients with multiple hospitalizations were used. This study suggests that the effect of gender in schizophrenia is strong enough to demonstrate significant differences when the stringent criteria of *DSM-III* are used, even given the relatively small sample size.

Since the original study was not designed to test for gender differences, explanatory tests were limited. However, the results show that gender differences begin in the early stages of the disorder, as suggested by the importance of premorbid functioning. In fact, premorbid functioning explained 50% of the effect of gender on outcome when a 1-year observation period was examined, although it was responsible for only 1.9% of the effect of gender on 10-year outcomes. (The analyses are available on request.) This is consistent with past studies which have shown that premorbid functioning has its strongest impact in the earlier stages of the disorder and then other factors become more prominent predictors of long-term outcome (23).

Previous work has also demonstrated a bivariate relationship between gender and premorbid functioning (20) and between premorbid functioning and outcome (9). That is, schizophrenic men have been found to have poorer premorbid histories than schizophrenic women, and poor premorbid history has been found to lead to poorer outcome. The results of the present study provide a synthesis of past bivariate findings by suggesting that the determinants of the greater frequency of poor premorbid functioning in schizo-

TABLE 2. Steps in Regression Analysis Depicting Change in the Effect of Gender on 5-Year Outcomes of 58 Male and 32 Female Schizophrenic Patients

	Rehospitalization (log transformed)							Length of Stay (log transformed)					
Predictor	b[a]	SE	t[b]	Univariate F	R^2	Multivariate F	Multivariate R^2	b[a]	SE	t[b]	Univariate F	R^2	Multivariate R^2
Step 1				5.55[c] (df=2, 87)	0.11	4.14[d] (df=4, 172)	0.18				7.64[c] (df=2, 87)	0.14	
Previous hospitalization	0.26	0.12	2.14[e]					0.38	0.16	2.41[e]			
Gender	*−0.30*	*0.13*	*−2.34*[d]					*−0.47*	*0.16*	*−2.90*[d]			
Step 2				5.13[d] (df=3, 86)	0.13	2.98[d] (df=6, 170)	0.21				4.18[d] (df=3, 86)	0.15	
Previous hospitalization	0.25	0.12	2.10[e]					0.38	0.16	2.37[e]			
Gender	*−0.26*	*0.13*	*−1.99*[g]					*−0.45*	*0.17*	*−2.65*[d]			
Premorbid functioning	0.07	0.06	1.20					0.04	0.08	0.49			
Step 3				2.85[d] (df=7, 82)	0.20	1.98 (df=14, 162)	0.27				3.29[d] (df=7, 82)	0.22	0.14[f]
Previous hospitalization (0 vs. 1)	0.23	0.12	1.80					0.32	0.16	1.98[e]			
Gender (0=male; 1=female)	*−0.25*	*0.13*	*−1.80*					*−0.40*	*0.18*	*−2.25*[e]			
Premorbid functioning	0.09	0.06	1.44					0.06	0.08	0.77			
Age	−0.009	0.01	−0.78					−0.006	0.01	−0.39			
Never married (0) vs. ever married (1)	−0.10	0.21	−0.48					−0.06	0.27	−0.23			
White collar (1) vs. unemployed (0)	0.39	0.16	2.42[d]					0.45	0.21	2.16[e]			
Blue collar (1) vs. unemployed (0)	0.21	0.17	1.24					0.42	0.22	1.88[g]			
Step 4 (all previous variables controlled)				2.34[d] (df=11, 78)	0.25	1.80[e] (df=22, 154)	0.37				3.11[d] (df=11, 78)	0.30	0.17[f]
Gender (0=male; 1=female)	*−0.25*	*0.14*	*−1.71*					*−0.39*	*0.18*	*−2.11*[e]			
Schizophreniform (1) vs. schizophrenia (0)	−0.07	0.19	−0.37					−0.14	0.24	−0.56			
Schizoaffective (1) vs. schizophrenia (0)	0.01	0.12	0.05					−0.27	0.25	1.10			
Psychotic symptoms	0.36	0.20	1.80					0.35	0.25	1.37			
Affective symptoms	0.11	0.12	0.87					0.32	0.16	2.04[e]			

[a] Regression coefficient representing change in log value of the dependent variable per unit change in the independent variable.
[b] $t=b/SE(b)=\sqrt{F}$; degrees of freedom for $t=n-k-1$, where n is the number of subjects and k is the number of predictors.
[c] $p<0.001$.
[d] $p<0.01$.
[e] $p<0.05$.
[f] R^2 adjusted for number of predictor variables and sample size.
[g] $p<0.06$.

phrenic men also may lead to poorer outcome for them than for schizophrenic women.

There are some limitations to the inclusion criteria used in this study, i.e., the age limit of 45 years and the family setting. Previous studies have found that for approximately 9% of schizophrenic women, the onset of the disorder occurs after 45 years of age, whereas this is true for few, if any, schizophrenic men (1, 3). Women with late onset have been found to express more paranoia than do men or women with early onset (24). This study did not include these women; however, if it had, differences in the course of illness between men and women would most likely have been enhanced rather than attenuated, since persons with paranoid schizophrenia have been found to have better outcomes than those with nonparanoid schizophrenia (25).

In addition, one might claim that schizophrenic patients who return to live in a family setting are different from schizophrenic patients in general. However, there is evidence from a number of studies that families are heavily relied on to take care of their members (10). In fact, it has been demonstrated that most patients return to their families while they are in the early stages of their illness (10), and it is usually only after patients have had several hospitalizations that families may separate from them. Since all patients in this study were in the early stages of the disorder, the family setting most likely did not bias the sample. In addition, our findings have been replicated

in a larger study, which used a representative sample of first-admission cases from Hanover, West Germany, and for which family setting was not an inclusion criterion (1987 paper by Angermeyer et al.).

The findings of this study demonstrate the validity of gender differences in the course of schizophrenia and the importance of the premorbid period for understanding these differences. Other factors that may be important in understanding the relationship of gender to outcome and that can be examined in future research include age at onset, family history, clinical expression, response to treatment, structural brain abnormalities, and illness behavior factors such as differences between the sexes in compliance with psychiatric treatment, perception of symptoms, help-seeking behavior, and tolerance of deviance by others (1–11, 13, 14, 26, 27). Finally, the findings of this study should be extended to other outcomes, since schizophrenic women have been found to exhibit a more favorable course in terms of psychopathology, social functioning, and overall prognosis than schizophrenic men. Further research on the relationship of gender to schizophrenia is needed, since the findings of this study have implications for the treatment of schizophrenia and may provide clues to etiology.

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Psychiatric Residents' Sexual Contact With Educators and Patients: Results of a National Survey

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In a national survey of PGY-4 psychiatric residents, 4.9% of the 548 respondents indicated that they had been sexually involved with psychiatric educators and 0.9% reported that they had been sexually involved with patients. Most residents reported no or minimal instruction in their residency programs about educator-resident and resident-patient sexual contact. The authors compare these results with those from previous surveys of psychologists. They discuss the need for expanding training curricula to include specific education on sexual exploitation.

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Although the code of ethics of the American Psychiatric Association (APA) explicitly prohibits sexual contact between psychiatrists and patients (1), there are no clear ethical guidelines regarding sexual contact between psychiatric educators (clinical supervisors, course instructors, advisors, or administrators) and psychiatric residents. In considering the ethical issues involved in teacher-student sexual relationships, the APA Ethics Committee pointed out that such relationships can be problematic because of substantial inequities in power and status:

> These relationships are commonly affected by transferences similar to those developed by patients, which involve adulation for the teacher that is easily mistaken for "love" (the crush). The transference further exaggerates the participants' inequality and makes these relationships very vulnerable to acting out. Thus, in various ways, sexual activity with students, even if it appears consenting, may well constitute exploitation of an unequal relationship for the teacher's own gratification. (2)

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In addition, the committee expressed concern that sexual involvement between a psychiatric resident and clinical supervisor may have adverse effects on the patients whose treatment is being supervised and inhibit the resident's understanding of sexualized transference/countertransference issues (2).

Surveys of clinical psychologists suggest that sexual involvement between psychology educators and graduate students may exert a "modeling effect" on later sexual exploitation of patients. In a nationwide survey of American Psychological Association division 29 (psychotherapy) by Pope et al. (3), 10% of the respondents reported that as students they had had sexual contact with their educators. Significantly more women (16.5%) than men (3%) reported sexual contact while they were students. Although the number of men engaging in sexual contact while students was too small for contingency table analysis, for the women sexual involvement during graduate education was statistically related to later sexual involvement with patients. Pope et al. also found that sexual contact in psychology programs appeared to be increasing, despite the finding that only 2% of the responding psychologists believed such relationships could be beneficial.

Glaser and Thorpe (4) found in a survey of female members of American Psychological Association division 12 (clinical psychology) that 22% of the recent doctorate recipients had been sexually involved with their psychology educators. The psychologists who acknowledged that they had had such contacts while students had a substantially more negative assessment of the experience when surveyed than they did during training. Almost all of the responding psychologists felt that psychology educator-student sexual contact during an ongoing work relationship was highly unethical.

In the absence of data on the sexual involvement between psychiatry educators and residents, we conducted a national survey of PGY-4 psychiatric residents. An attempt was made to document the prevalence of educator-resident and resident-patient sexual contact. We predicted gender differences in both attitudes and practices and differences between the involved residents and their peers.

TABLE 1. Residents' Assessment of Their Education on Educator-Resident and Psychiatrist-Patient Sexual Contact

Response	Residents (N=546) N	%
Education on educator-resident sexual contact		
Thorough	3	0.5
Some	23	4.2
Very little	112	20.5
None at all	408	74.7
Education on psychiatrist-patient sexual contact		
Thorough	66	12.1
Some	204	37.4
Very little	192	35.2
None at all	84	15.4

METHOD

The 46-item questionnaire contained five items on the demographic characteristics of the respondents, three items on attitudes toward psychiatric educator-resident and resident-patient sexual relationships, two items on residency education regarding such relationships, two items on knowledge of APA ethical guidelines regarding such relationships, and 34 items on the respondents' personal experiences with educators and patients. Sexual contact was defined as contact "intended to arouse or satisfy sexual desire" (5–7). "Psychiatric educator" referred to "any person who served as a clinical supervisor, course instructor, advisor or administrator" in the respondent's residency program. Most of the questions required a precoded, forced-choice response or a numerical specification. Space was provided for additional comments.

The questionnaire, a one-page cover letter, and a stamped, addressed return envelope were mailed out in September 1986 to all 1,113 psychiatric residents who were identified as PGY-4 trainees in the American Medical Association Masterfile; 723 (65.0%) were male, and 390 (35.0%) were female. No other demographic information about the sample was available. The cover letter explained the purpose of the study and the procedures for establishing complete confidentiality and anonymity. The respondents were asked to return the questionnaire by Nov. 30, 1986. A postcard reminder was mailed out 2 weeks after the questionnaire.

The anonymous responses were keypunched and tabulated. Unless otherwise noted, chi-square tests (without continuity correction) were used in the analysis. Fisher's exact tests (two-tailed) were used in all cases for which the expected cell frequencies were too small for chi-square analysis to be an accurate test of significance.

RESULTS

Of the 1,087 questionnaires that reached their destinations, 548 (50.4%) were completed and returned by the respondents. Of these 548 respondents, 321 (58.6%) were male, 225 (41.1%) were female, and two (0.4%) did not specify their genders. Proportionately more women (57.7%) than men (44.4%) responded to the questionnaire ($\chi^2=16.8$, df=1, $p<0.001$). Not all questions were answered by all respondents, so the number of respondents on which the following percentages were based varies.

Educator-Resident Sexual Relations

The great majority of respondents believed that sexual contact between a psychiatric educator and resident who have an ongoing work association is inappropriate (74.2%, N=402) and usually harmful to the work relationship (80.0%, N=436). Written comments from a number of respondents indicated that there was considerable concern about the possibility of exploitation in such relationships. For example, a 31-year-old male resident wrote, "I consider the position of faculty over residents one which can easily be abused .... Guidelines for 'due process' [are] no protection."

By contrast, if the resident and educator *do not* have an ongoing work relationship, most residents (79.4%, N=432) believed that sexual contact could be appropriate. No gender differences emerged on any of these variables.

Less than 1% of the respondents (N=3) reported that educator-resident sexual contact had been addressed thoroughly during residency training (table 1). Two-thirds of the respondents (67.6%, N=361) were correct in their belief that APA does not have an official policy on sexual contact between psychiatric educators and residents (table 2).

Twenty-six (4.9%) of the 527 residents who answered the question acknowledged having had sexual contact with psychiatric educators. We compared these residents with their peers on all variables and found no differences between these two groups. The respondents who indicated sexual involvement with educators included 6.3% of the women (N=14) and 3.9% of the men (N=12) who answered the question. Fourteen of the involvements occurred between female residents and male educators, nine were between male residents and female educators, and two were between male residents and male educators; one resident did not specify the genders of the parties involved.

More female residents (nine of 14) than male residents (two of 11) had been involved in sexual contacts initiated by educators (Fisher's exact test, two-tailed, p=0.04). The educators were older than the residents in 19 cases. The mean±SD age difference between the male educators and female residents (N=13) was 12.8±8.6 years, while the difference between the female educators and male residents (N=5) was 3.0±1.6 years. The sexual contact began early in training in the majority of cases: seven of the residents were in PGY-1, five were in PGY-2, eight were in PGY-3, and two were in PGY-4. The educator's status vis-à-vis the

TABLE 2. Residents' Knowledge of APA Policies on Educator-Resident and Psychiatrist-Patient Sexual Contact

Response	Residents N	Residents %
"To the best of your knowledge, what is the APA's position on sexual contact between psychiatric resident and psychiatric educator?" (N=534)		
Sexual contact is permissible during an ongoing work relationship in certain special circumstances	2	0.4
Sexual contact is permissible only if it occurs outside of scheduled work or supervisory sessions	16	3.0
Sexual contact is permissible only if the work relationship has terminated	95	17.8
Sexual contact is not regulated by the APA code of ethics	361	67.6
Sexual contact is unethical under any circumstance	60	11.2
"To the best of your knowledge, what is the APA's position on sexual contact between psychiatrist and patient?" (N=545)		
Sexual contact is permissible during treatment sessions in certain special circumstances	0	0.0
Sexual contact is permissible only if it occurs outside of scheduled treatment sessions	0	0.0
Sexual contact is permissible only if treatment has terminated	86	15.8
Sexual contact is not regulated by the APA code of ethics	6	1.1
Sexual contact is unethical under any circumstance	453	83.1

resident at the onset of the sexual contact was clinical supervisor in seven cases, course instructor in two cases, administrator in two cases, advisor in one case, and unspecified in 14 cases. Characteristics of the resident-educator sexual contacts are presented in table 3.

Although 11 residents (including the four who were currently married to their former educators) were pleased about the sexual involvement overall, there was a trend toward more negative assessments over time (table 3). Four residents indicated that they experienced the contacts as sexual harassment. For example, a female resident who acknowledged sexual involvement with a clinical supervisor during PGY-1 wrote, "I wish I had not . . . . I was young, scared, and naive." A 29-year-old woman in PGY-3 expressed anger that she had been harassed by a 52-year-old research advisor who sought to date her while helping her on a paper. "He attempted to disrobe me . . . without my consent. [The experience] derailed my career for 2 years, and I am still in the process of getting it back on course," she wrote.

TABLE 3. Characteristics of Sexual Contacts Between Psychiatric Educators and 26 Residents

Characteristic of Sexual Contact	Number of Residents
Initiator	
Resident	0
Educator	11
Both	14
No response	1
Duration of sexual contact	
One time only	6
<3 months	5
3–11 months	4
1–3 years	6
>3 years	4
No response	1
Did contact begin during working relationship?	
Yes	11
No	14
No response	1
Feelings about contact at onset[a]	
Appropriate	16
Helpful	3
Caring	11
Inappropriate	2
Harmful	1
Exploitative	2
Effect on working relationship at onset	
Beneficial	2
Mixed	2
Harmful	1
No effect	8
Other or no response	13
Feelings about contact currently[a]	
Appropriate	9
Helpful	3
Caring	8
Inappropriate	7
Harmful	7
Exploitative	7
Current effect on working relationship	
Beneficial	5
Mixed	4
Harmful	6
No effect	5
Other or no response	6
Current status of relationship	
No contact	7
Continued sexual contact, no work contact	4
Continued work contact, no sexual contact	6
Continued sexual and work contact	3
Other or no response	6
Has sexual contact resulted in marriage or committed relationship?	
Yes	6
No	19
No response	1
Overall feelings about sexual contact	
Pleased	11
Mixed	9
Regret	4
No response	2

[a]Multiple responses permitted.

Psychiatrist-Patient Sexual Relations

Most respondents believed that psychiatrist-patient sexual contact is inappropriate (98.7%, N=539) and usually or always harmful to patients (91.2%, N=497). Many commented spontaneously that psychiatrists should seek supervision if they are considering sexual involvement with patients. For example, a 36-year-old male psychiatrist wrote, "Sexual attraction is very common, as is mutual attraction. It is called transference and countertransference. It calls for interpretation, not orgasm."

TABLE 4. Characteristics of Residents and Patients in Five Cases of Therapist-Patient Sexual Contact

	Resident					Patient	
Case	Sex	Marital Status	Age (years)	Year	Sexual Orientation	Sex	Age (years)
1	M	Single	33	PGY-4	Heterosexual	M	36
2	M	Married	31	PGY-4	Heterosexual	F	25
3	F	Separated or divorced	32	PGY-1	Heterosexual	M	31
4	M	Single	25	Third-year medical student on psychiatry rotation	Homosexual	M	20
5	M	Married	—	—	Heterosexual	—	—

Twelve percent of the respondents (N=66) indicated that issues concerning therapist-patient sexual contact had been thoroughly discussed in their residency training programs (table 1). Eighty-three percent (N=453) knew that APA considers psychiatrist-patient sexual contact unethical under any circumstance (table 2). The respondents commented on the need for expanded educational programs on this issue. For example, a 30-year-old female resident wrote, "We just had a discussion of this topic in Journal Club—the first public discussion I've heard. As with impaired physicians it needs attention (not just judgmental pronouncements) by all residency training programs and the APA." Others indicated that their training about the issues came through policy statements which were not explained or discussed. "Although this was not thoroughly addressed in our residency, the message I have is a very black and white one, i.e., no sex with patients or students," stated one 35-year-old male respondent. Two respondents indicated that their residency training directors had established clear prohibitions against sexual contact with patients. One wrote, "During intern rotation, our residency director told us any resident having sexual relations with a patient would be 'fired on the spot.'" The other reported that "the only time anything of this sort was mentioned was when the director of our training program handed out a xerox of the APA's position paper, and said you can get sued for sexual contact with patients and told us not to, period."

Sexual attraction to one or more patients was acknowledged by 72.1% of the respondents (N=392). Significantly more male (85.7%) than female (52.0%) respondents acknowledged such attraction ($\chi^2=74.3$, df=1, $p<0.001$). Most of those indicating attraction to patients (78.3%, N=307) had discussed their feelings with their supervisors. The residents who had addressed these issues in supervision were more likely than the other residents who had been attracted to patients to have been in psychotherapy or psychoanalysis (74.0% versus 52.1%; $\chi^2=15.86$, df=1, $p<0.001$) and were more likely to have had a thorough residency education regarding therapist-patient sexual contact (16.9% versus 5.3%; $\chi^2=7.88$, df=1, $p=0.005$). Residents who indicated at least some education regarding educator-resident sexual contact (100%) were also more likely than those with little or no such education (74.7%) to have discussed their feelings about patients with supervisors ($\chi^2=5.99$, df=1, $p<0.05$).

In their written comments, the residents strongly supported discussing attraction to patients in supervision. For example, a 34-year-old female resident wrote, "I was aware of the potential for sexual attraction to a male patient which I discussed with a supervisor, which was probably preventative." Another woman, 28 years old, said, "I've been attracted to an educator, and talking it through without acting on it helped a lot. I learned from it. Likewise, I learned from understanding my attraction to patients in supervision but *not* acting on it." Some residents indicated that they wanted to discuss these feelings in supervision but needed more encouragement from supervisors. "I think educators should bring up the topic in the course of supervision and not leave it up to the resident," said a 30-year-old female resident. A 29-year-old male resident wrote, "It is almost impossible for gays to discuss such issues with supervisors, yet straight men are actively encouraged to do so."

Of the 392 residents who acknowledged sexual attraction to patients, 10.7% (N=42) believed that one or more patients had been aware of their attraction. Twenty-five residents thought that this had occurred with only one patient, 14 with two to nine patients, two with 10 patients, and one with 30 patients. Thirty-five (83.3%) of the 42 residents who believed patients had been aware of their attraction had discussed their feelings with supervisors.

Five residents (0.9% of the 539 who responded to the question) acknowledged having had sexual contact with patients (see table 4). The sexual contact had begun during treatment or within 11 months of termination in each of the four cases for which the offending residents provided information. Only one resident discussed the sexual contact with a supervisor. Each of the four residents who answered the question currently regretted the sexual involvement with a patient. None of the residents who had been sexually involved with an educator acknowledged sexual contact with a patient.

DISCUSSION

This survey demonstrates that most PGY-3 psychiatric residents consider sexual contact between a psy-

chiatric educator and resident inappropriate and harmful to an ongoing work relationship. In addition, psychiatric residents endorse an absolute prohibition against sexual contact with patients. However, very few residents report more than minimal education about issues of sexual exploitation in their residency training programs. Less than 1% of the respondents in our study felt thoroughly educated about educator-resident sexual contact, and only 12.1% believed they had received a thorough education on therapist-patient sexual contact. These findings are similar to reports on recent graduates of doctoral psychology programs (4), of whom only 3% felt that educator-student sexual involvement had been thoroughly discussed during training and 22% believed that therapist-patient involvement had been thoroughly addressed.

Despite the lack of training in these issues, most residents appear to have some understanding of the power dynamics of unequal relationships. Whereas 79.4% of the residents considered educator-resident sexual contact permissible if there is no ongoing work relationship, 74.2% considered such relationships inappropriate during a work association.

Only 4.9% of the psychiatric residents acknowledged sexual involvement with psychiatric educators. Substantially fewer female psychiatric trainees (6.3%) than recent female graduates of doctoral psychology programs (22%–25%) had been involved with educators (3, 4). Our data also differed from those from the psychology studies in that the likelihood of sexual involvement with an educator was not gender-specific. Pope et al. (8) suggested that because competition for admission to and employment after psychology training programs is so severe, psychology students may be reluctant to refuse sexual advances from educators. Perhaps the greater employment opportunities in psychiatry allow female psychiatric residents to decline sexual advances with less anxiety than their peers in psychology.

Since our respondents were trainees at the time they completed the questionnaire, we were not able to assess the "modeling effect" of educator-resident sexual contact on later sexual involvement with patients. Long-term follow-up of this population would be needed to evaluate this possibility. A longitudinal study would also provide information about the effects of sexual contact with educators on the careers of psychiatric residents. Glaser and Thorpe (4) found that female psychologists described their sexual involvement with educators as substantially more exploitative and unethical *after* they had completed training. The residents in our study also showed a trend toward more negative assessments over time.

It is encouraging to see that most of the residents in our survey who experienced sexual attraction to patients discussed their feelings in supervision. It is also noteworthy that the residents who were educated about sexual contact with patients or educators were more likely to discuss their attraction to patients with supervisors. However, 16.7% of those whose patients were aware of their attraction had *not* discussed their feelings in supervision. It is also worrisome that several residents reported that 10 or more patients had been aware of their attractions. We did not ask how the patients had become aware of the attractions, but the prevalence of awareness raises questions about the quality of supervision regarding eroticized countertransference feelings. Psychologists in a recent national survey reported that the therapy was more likely to be harmed or impeded if the patient was aware of the attraction (9). Some residents in our survey indicated that they would like their supervisors to inquire about sexual countertransference feelings and to provide clear directives for managing these feelings in treatment.

The APA Ethics Committee has taken an important step by stating in its newsletter that sexual contact between supervisors and supervisees may be unethical because of its potential negative impact on the patient whose treatment is being supervised (2). However, a newsletter statement does not constitute an official policy position. The findings of this survey indicate that a major educational effort regarding the potential abuse of professional power is needed in all residency training programs. We recommend that APA amend its *Principles of Medical Ethics* to specify that sexual contact between a psychiatric educator and resident is unethical as long as the educator has authority over the resident. We recognize that such authority may be of long duration, continuing as long as the educator is in a position to advance or obstruct the student's professional career. We further recommend the development of curricula for both residents and faculty on the dynamics of sexual exploitation, the psychological consequences of inequality, and the management of eroticized transference and countertransference feelings.

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Refining the Diagnosis of Schizophreniform Disorder

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Schizophreniform disorder, a potentially useful construct, is difficult to operationalize either for clinical or research purposes. According to DSM-III-R, *schizophreniform disorder is descriptively identical to schizophrenia, differing only in duration of symptoms. This study suggests several features that, at initial examination, differentiate schizophreniform disorder from schizophrenia, such as higher* DSM-III *axis V ratings, lack of flattened affect, and better rapport with the examiner. The data suggest that when defined according to appropriate clinical criteria, schizophreniform disorder can be distinguished from either schizophrenia or affective disorder.*

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The observation that schizophrenic outcome is highly variable (1–6) has stimulated the investigation of clinical patterns which predict a favorable prognosis. Langfeldt's (7) differentiation of schizophreniform psychosis from typical schizophrenia is one of the better known attempts in this area. The concepts of schizophreniform disorder described in *DSM-III* and *DSM-III-R* are almost identical: both systems use symptom duration as the major criterion to differentiate the illness from schizophrenia. According to the *DSM-III-R* definition of schizophreniform disorder, "The essential features of this disorder are identical with those of schizophrenia, with the exception that the duration, including prodromal, active and residual phases, is less than six months" (p. 207). Studies of the clinical usefulness of the schizophreniform diagnosis have yielded equivocal results. Using a chart review, Fogelson et al. (8) selected patients qualifying for a *DSM-III* diagnosis of schizophreniform disorder. These authors argue that the patients' past histories, family histories, and associated laboratory findings suggested that they were really suffering from affective illnesses; their findings suggest that the schizophreniform episode experienced by their subjects was an acute psychotic illness without affective symptoms, which alternated with more typical periods of mania and depression. Coryell and Tsuang (9) presented data demonstrating that schizophreniform disorder exhibits a clinical course midway between schizophrenia and affective disorder, and Kendler et al. (10, 11) suggested that schizophreniform disorder belongs within the "schizophrenia spectrum."

The centrality of symptom duration as a criterion for the diagnosis of schizophreniform disorder creates problems in research and clinical practice. Whether a clinician happens to see someone with a duration of symptoms of more or fewer than 6 months often depends more on sociocultural factors affecting help seeking than on the illness itself (12). Thus, the 6-month duration criterion for establishing a diagnosis of schizophrenia fails to do justice to Langfeldt's concept of insidious onset and evidence of personality deterioration. A second major problem with the *DSM-III* and *DSM-III-R* definitions of schizophreniform disorder is that the diagnosis can be made with confidence only in retrospect, i.e., if recovery takes place within a relatively short period of time. As *DSM-III-R* points out, even if someone whose schizophrenia-like symptoms are assessed when he or she has been suffering the disorder for fewer than 6 months, ". . . there is no certainty that the person will actually recover from the disturbance within the required six-month period" (p. 208). Under these conditions, clinicians are counselled to make a diagnosis of schizophreniform disorder, "provisional." This is unfortunate since prognosis ideally should be inherent in diagnosis and the ability to forecast course part of the clinician's armamentarium. The inclusion of "good prognostic features" in the consideration of this diagnosis in *DSM-III-R* marks an important step in refining the construct of schizophreniform disorder by means of unique and explicit criteria.

The current study, one of a handful of prospective inquiries, describes features that distinguish schizophreniform patients who recovered from their illness

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from others whose symptoms persisted long enough for them to be classified schizophrenic.

The changes from *DSM-III* to *DSM-III-R* regarding the schizophreniform category include the stipulations that the clinical picture must not meet the criteria for brief reactive psychosis and that there is no evidence that an organic factor initiated and maintained the illness. *DSM-III-R* also includes a subcategory of good prognostic features, which includes at least two of the following: 1) onset of prominent psychotic symptoms within 4 weeks of first noticeable change in usual behavior or functioning; 2) confusion, disorientation, or perplexity at the height of the psychotic episode; 3) good premorbid social and occupational functioning; and 4) absence of blunted or flat affect (p. 208). Because our study was initiated before the publication of *DSM-III-R*, we did not systematically collect data about all four prognostic features thought to be associated with a favorable course; however, we present data about the last two—premorbid functioning and blunted affect. In addition, we considered the prognostic significance of poor rapport with the examiner. Although not included in *DSM-III-R* categorizations of schizophrenia or schizophreniform disorder, many clinicians have felt that poor rapport is an ominous clinical sign (1), while some research (13) suggests that it is a behavioral interaction characteristic of schizophrenia.

METHOD

The research we report is part of an investigation of biological and psychosocial factors implicated in the course of first-episode schizophrenia: The markers and predictors of schizophrenia study, initiated at the University of British Columbia in 1982, utilizes a sampling framework consisting of all persons experiencing a first episode of psychosis in the greater Vancouver area from July 1982 through October 1984. To minimize selection bias, we extended recruitment beyond the mental health care system to establish a community-wide network of hospitals, medical and social service agencies, and private psychiatric and family practice settings at which persons suffering a psychotic disorder might appear. To avoid missing potential cases, we supplied the referral agencies with very broad inclusion criteria. Agencies and practitioners were asked to refer anyone experiencing hallucinations or delusions, displaying grossly disorganized behavior, showing marked thought and speech disorder, or having two or more of the following: marked loss of drive, social withdrawal, severe excitement, overwhelming anxiety or fear, or gross self-neglect. Subjects were also required 1) to have lived in the Vancouver metropolitan area at least 6 months, 2) to be between the ages of 15 and 54 years, and 3) not to demonstrate organic cerebral illness, severe mental retardation, chronic physical disorder, or chemical dependence. During the intake period, 300 potential subjects were identified by community referral sources; 175 were recruited, and 125 either refused to participate in the study or fled the treatment system before we could approach them. Aggregate level analyses comparing interviewed to lost subjects revealed no differences in age, sex, or diagnosis received in treatment setting.

After a subject signed a form indicating consent to participate in the study, one of the project clinicians—either a psychiatrist or Ph.D. clinical psychologist—conducted an interview, utilizing the Present State Examination (PSE), ninth edition, a semistructured clinical interview designed to yield reliable psychiatric diagnoses (14). Using a variety of instruments, research assistants then interviewed the subjects. They also obtained ancillary information from hospital charts. Each subject was asked to enroll at least one significant other, preferably a first-degree relative, in the study.

After the gathering of all intake data from subjects, treatment agencies, and significant others, the project staff, including at least one psychiatrist and one clinical psychologist, met to determine whether symptoms and signs relevant to the various *DSM-III* diagnoses were present. The method resembles a best-estimate diagnosis (15) in assuming that the best diagnosis is the one made on the basis of the most complete information. In addition, we addressed the problem of reliability. Although the explicit criteria of *DSM-III* facilitate reliability, it is compromised by human failure to consistently follow diagnostic rules. Our case conferences addressed this problem by imposing a procedure whereby clinicians addressed each criterion specified for each possible diagnosis listed in the *DSM-III* to decide whether a code of "present" or "absent" was appropriate; it was then possible to strictly follow the decision rules supplied in *DSM-III* to arrive at diagnoses on each of the five axes. Since the study predated *DSM-III-R*, axis V ratings followed the *DSM-III* system, which encompasses social relations, occupational functioning, and use of leisure time but, unlike *DSM-III-R*, does not take symptoms into account. We assessed agreement among the project clinicians for the first 15 cases entered into the study. Among differing pairs of clinicians the kappa coefficients for axis I psychiatric diagnoses varied from .74 to .96. There were too few cases receiving axis II and III diagnoses to merit analysis. Correlation coefficients for axis IV and V were 0.81 and 0.89, respectively. Having achieved these acceptable levels of interrater reliability, we moved to consensus diagnosis as a method of choice for all study cases. Several authorities have reported that consensus diagnoses prove more reliable than single-rater diagnoses when complex and multifaceted clinical data are used (16, 17).

Nine months after intake, each subject was reassessed with 1) the SCL-90-R (18), a widely used symptom checklist, 2) selected portions of the NIMH Diagnostic Interview Schedule (DIS) (19), a structured, lay-administered interview that yields *DSM-III* diag-

noses, and 3) a series of questions covering illnesses after the initial episode, work history, and social relations within the past 9 months. Eighteen months after intake, we reinterviewed subjects with the PSE, readministered the SCL-90-R, and added the Social Adjustment Scale (20), a structured interview yielding a set of scales measuring adaptation in such major life areas as work, leisure time, and social relationships. During the intake, 9-, and 18-month interviews, we asked subjects about their overall happiness: "Taking all things together, how would you say things are these days—Would you say you are very happy [scored as 1], pretty happy [scored as 2], not too happy [scored as 3]?" The question, which possesses an appealing face validity, has seen extensive use as a measure of well-being (21, 22). We reinterviewed the subjects' significant others for ancillary information and searched treatment files for each of the general hospitals with psychiatric services in the greater Vancouver area, the Provincial Mental Hospital, and the community mental health care system to document any illness episodes as well as treatment interventions.

Project staff, with at least two clinicians present, used the results from the SCL-90-R, DIS, and PSE and other interview data to rate each subject's overall functioning on the Global Assessment Scale (GAS) (23) at 9 and 18 months after intake and to assign diagnoses at these points. Responses to the overall happiness question and the Social Adjustment Scale were not, however, made available for these assessments. At 9 months after intake, it became clear that some of the subjects, their symptoms having resolved in fewer than 6 months from onset, no longer qualified for a psychiatric diagnosis on clinical grounds. Others with persistent symptoms could now be reclassified as schizophrenic or in a few instances as having affective disorder. Using only the diagnoses arrived at during the clinical conferences at 9 months, one of the project psychiatrists (J.A.E.F.) assigned each subject to one of five categories: "true" schizophreniform (clinically recovered within 6 months), nonrecovered schizophreniform (rediagnosed as schizophrenic), schizophrenic, affective disorder, other.

RESULTS

Among the 175 subjects originally admitted to the study, 159 were retained for the current analyses. Of 29 subjects diagnosed as schizophreniform at intake, eight (about 30%) recovered and 18 were classified as schizophrenic at the 9-month follow-up. The project clinical staff assigned a diagnosis of affective disorder to the three remaining schizophreniform subjects with persistent symptoms. Since they are such a small group, subjects rediagnosed as having affective disorder have not been included in the analyses we present. Some of the attrition in the overall sample (the difference between 159 and 175) was due to the subjects' moving, refusing to be reinterviewed, or dying. A few other cases were excluded; since we were interested in assessing the characteristics of schizophreniform disorder and comparing them with the characteristics of schizophrenia and affective disorder, we did not include a small number of subjects who received an intake diagnosis of atypical, paranoid, or schizoaffective psychosis. Thus, our two comparison groups consisted of subjects with schizophrenia (N=60) and affective disorder (N=73).

The mean±SD age of our subjects was 24.41±7.1 years. An analysis of variance indicates that the affective disorder group had a higher mean±SD age than the other three groups (recovered schizophreniform, 21.3±4.6 years, range 16–30; nonrecovered schizophreniform, 22.3±5.0, range 16–33; schizophrenia, 23.2±6.3, range 15–44; affective disorder, 26.3±7.9, range 17–50) ($F=3.59$, $df=3, 156$, $p<0.05$; Newman-Keuls test, $p<0.05$).

The remainder of the analyses examine characteristics differentiating recovered schizophreniform subjects from subjects in the three other diagnostic categories. For the first comparison group, nonrecovered schizophreniform subjects, our working hypothesis was that persons in this category are clinically the same as the group initially diagnosed schizophrenic, although the circumstances that brought them to the attention of the mental health treatment system may have differed. Thus, the nonrecovered schizophreniform subjects should resemble the first-episode schizophrenic subjects while the recovered group should differ from the schizophrenic group, particularly with respect to those characteristics specified in *DSM-III-R*. Since some have contended that schizophreniform disorder is best conceptualized as affective disorder (8), the latter is retained as a comparison group of interest.

The results of our determination of the validity of the diagnostic groupings on the basis of three outcome measures, the GAS, overall happiness, and the Social Adjustment Scale, are presented in table 1. For all the comparisons, the schizophreniform group who recovered demonstrated better adjustment than the nonrecovered schizophreniform or the first-episode schizophrenic groups. Scores for the latter two groups were essentially identical. Recovered schizophreniform subjects scored the highest on the GAS, followed by the affective disorder group. On the Social Adjustment Scale, the recovered schizophreniform and affective disorder groups had similar scores, which indicated higher levels of social and leisure adaptation than the scores for the nonrecovered schizophreniform and the schizophrenic groups. The social adjustment scores for the other two groups were once again similar. The scores of the recovered schizophreniform subjects with respect to overall happiness indicated that they were happier than the subjects in the other diagnostic categories, although the differences did not reach conventionally accepted levels of statistical significance, possibly because the use of a single item among small groups limits statistical power.

Of the four *DSM-III-R* good-prognosis criteria, our

TABLE 1. Eighteen-Month Follow-Up Scores on Three Outcome Measures for Four Diagnostic Groups

Diagnostic Group	GAS[a] Mean	GAS[a] SD	Overall Happiness[b] Mean	Overall Happiness[b] SD	Social Adjustment Scale[c] Mean	Social Adjustment Scale[c] SD
Recovered schizophreniform (N=8)	76.5	9.8	1.7	0.52	20.6	2.4
Nonrecovered schizophreniform (N=18)	38.1	12.3	2.3	0.49	28.1	5.5
Schizophrenic (N=60)	44.5	19.7	2.1	0.62	26.3	4.0
Affective disorder (N=73)	61.2	20.8	2.0	0.66	23.7	6.0

[a]High score indicates good functioning and few or no symptoms. Significant difference among groups (F=12.9, df=3, 113, p<0.001; recovered schizophreniform>affective>all others, p<0.05, Newman-Keuls test).
[b]Low score indicates high positive affect (1=very happy, 2=pretty happy, 3=not too happy). Nonsignificant difference among groups (F=2.2, df=3, 104, p<0.10).
[c]Low score indicates good social adjustment. Significant difference among groups (F=4.5, df=3, 95, p<0.005; recovered schizophreniform=affective>nonrecovered schizophreniform=schizophrenic, p<0.05, Newman-Keuls test).

TABLE 2. Highest Level of Premorbid Functioning Among Four Diagnostic Groups

Diagnostic Group	Intake *DSM-III* Axis V Rating[a]: Good or Better N	Good or Better %	Fair or Worse N	Fair or Worse %
Recovered schizophreniform (N=8)	7	88	1	13
Nonrecovered schizophreniform (N=18)	3	17	15	83
Schizophrenic (N=60)	15	25	45	75
Affective disorder (N=73)	41	56	32	44

[a]χ^2=24.7, df=3, p<0.001.

TABLE 3. Intake PSE Ratings of Restricted Affect and Poor Rapport Among Four Diagnostic Groups

Diagnostic Group[a]	Restricted Affect[b]: Yes N	Yes %	No N	No %	Poor Rapport[c]: Yes N	Yes %	No N	No %
Recovered schizophreniform (N=8)	2	25	6	75	1	13	7	87
Nonrecovered schizophreniform (N=16)	9	56	7	44	6	38	10	63
Schizophrenic (N=58)	33	56	26	44	18	31	40	69
Affective disorder (N=72)	11	15	61	85	9	13	63	88

[a]The number of subjects varies because of missing data.
[b]χ^2=27.0, df=3, p<0.001.
[c]χ^2=9.2, df=3, p<0.05.

data furnish a commentary on two: premorbid functioning and absence of blunted or flat affect. For each subject, we recorded *DSM-III* axis V ratings of the best level of premorbid occupational, social, and leisure time functioning attained during the year before the illness. An analysis of variance comparing axis V mean±SD scores revealed significant differences among the groups (recovered schizophreniform, 2.9±0.64; affective disorder, 3.5±1.2; nonrecovered schizophreniform, 4.0±0.77; schizophrenic, 4.5±1.36) (F=11.2, df=3, 155, p<0.001). Higher scores indicate greater pathology. Although the recovered schizophreniform group appears to have the highest premorbid functioning level, the differences between their scores and the scores of the affective disorder group did not reach statistically significant levels when assessed with the Newman-Keuls test. However, both the recovered schizophreniform and the affective disorder groups had significantly higher mean scores on axis V than the schizophrenic and the nonrecovered schizophreniform groups (p<0.05, Newman-Keuls test); the mean scores of the latter two groups did not differ significantly from each other. The axis V data are presented in table 2 with ratings of superior, very good, and good collapsed into one category (good or better) and fair, poor, very poor, and grossly disorganized collapsed into a second (fair or worse). The distribution of the collapsed categories in table 2 suggests that in the year before their index illness good-prognosis schizophreniform subjects had obtained the highest level of occupational, social, and leisure functioning, followed by affective disorder subjects, schizophrenic subjects, and finally the nonrecovered schizophreniform subjects. Only one of the recovered schizophreniform subjects failed to attain a good or better level of premorbid functioning; the rating in that subject was fair.

The PSE calls for the clinician to rate the presence or absence of an item called "restricted affect," which is defined by rating instructions as "expressionless face and voice, uniform blunting whatever the topic of conversation, indifference to distressing topics, whether delusional or normal." Table 3 demonstrates that although more than half of the schizophrenic and nonrecovered schizophreniform subjects demonstrated restricted affect during the initial illness, it was rarely observed among the affective disorder or the good-prognosis schizophreniform subjects. The intake PSE ratings of poor rapport among the four diagnostic groups are also illustrated in table 3. During their initial episode of illness, twice as many nonrecovered

schizophreniform and schizophrenic subjects than recovered schizophreniform or affective disorder subjects displayed poor rapport.

DISCUSSION

Among a group of schizophreniform patients diagnosed according to strict *DSM-III* criteria, about 30% recovered in fewer than 6 months after the onset of their illness. Eighteen months after their initial episode of psychosis, the recovered schizophreniform group displayed better adjustment than 1) a group initially diagnosed as schizophreniform who were rediagnosed as schizophrenic, 2) a group originally diagnosed as first-episode schizophrenic, and 3) a group with affective disorder. The 18-month follow-up GAS ratings may be criticized for bias because they were not determined independently of the 9- and 18-month diagnoses. However, the overall happiness and the Social Adjustment Scale scores, obtained from self-report checklists not available to the research group at the time they made their diagnoses, confirm the impression that, 18 months after a first-episode of illness, the recovered schizophreniform group functioned at a much better level than the other subjects.

Our findings support the usefulness of the clinical criteria currently included in *DSM-III-R* to help refine the diagnosis of schizophreniform disorder. A rating of good or better on *DSM-III* axis V proved a powerful predictor, helping to differentiate schizophreniform disorder from schizophrenia and from affective disorder. The clinical observation of whether affect is retained and the clinician's assessment of rapport during the interview also possess prognostic value.

An unpublished study by Bassett et al. has demonstrated that, despite attestations to the contrary, when clinicians use *DSM-III* in everyday practice, they rarely record anything other than an axis I diagnosis. One reason may be that the clinical utility of axes II–V has not been well-demonstrated. Observations such as our own, that an easily obtained rating on axis V helps distinguish psychotic illnesses with good prognosis from those with poor outcome, should supplement rote learning of the contents of diagnostic manuals, thus making the adoption of the complete diagnostic schemes advanced in *DSM-III* and *DSM-III-R* maximally effective. These data as well as reports by others (24, 25) demonstrate the clinical utility of the *DSM-III* rating of premorbid social, occupational, and leisure functioning, a considerably different dimension from axis V of *DSM-III-R*, a scale whose scoring is heavily weighted by symptoms. In our experience, the inclusion of symptoms called for in arriving at a GAS score (the scale on which *DSM-III-R* axis V is based) not uncommonly alters the rating a subject would receive if he or she were judged solely on the basis of functioning; although useful for some purposes, GAS ratings, which combine psychiatric symptoms with social and occupational adjustment, may fail to do justice to the complexities of psychosocial adjustment (26, 27). *DSM-III* axis V has been criticized because the basis for arriving at ratings is less than optimally clear (28, 29) and the reliabilities obtained in clinical settings have proved to be lower than those achieved in research field trials (30, 31). Nevertheless, the conceptual appeal and clinical usefulness of *DSM-III* axis V suggest that attempts to improve its operationalization (31) should have received a fair trial before replacing it with an instrument of perhaps superior reliability but possibly lower prognostic utility.

Other studies assessing the clinical distinctiveness of schizophreniform disorder have produced equivocal and even conflicting conclusions (8–11, 32). Lack of diagnostic homogeneity probably accounts for some of the confusion in the research literature. Our data suggest that the use of a 6-month duration criterion with no additional inclusion features produces heterogeneity; persons with typical schizophrenia and affective disorder are placed in the same category as good-prognosis "true" schizophreniform subjects. In our series, 70% of the schizophreniform subjects diagnosed according to the criterion of duration of symptoms were suffering from schizophrenia. Any research series that contains a similar proportion of misdiagnosed schizophreniform subjects would probably produce results favoring a "schizophreniform equals schizophrenia" formulation. Our true schizophreniform subjects followed a course very different from that of the schizophrenic subjects and during the acute phases of their illness were distinguished from schizophrenic subjects by good prognostic features. Although the clinical course demonstrated by the schizophreniform subjects was closer to that of persons with affective disorder than schizophrenia, it would be premature to conclude that this condition is a type of affective disorder. Although differences were not always statistically significant, consistent trends in the data suggest that the prognosis for schizophreniform disorder is better than that for affective psychosis. The markers and predictors of schizophrenia study is investigating the clinical course of these subjects over a longer term to determine whether the trends already noted become stronger over time and to examine whether any of our first-episode true schizophreniform subjects develop other forms of psychiatric illnesses, e.g., whether they, like the subjects of Fogelson et al. (8), will experience episodes of affective illness. As a further examination of the utility of the concept, future studies of schizophreniform disorder, more clearly and explicitly defined than has been the case, should focus on conceptualizing clinical features predicting good prognosis, familial patterns, and associated features of the illness as well as on collecting data about the clinical course of the disorder. Since true schizophreniform disorder seems to be a rare condition, multicenter studies may have to be considered.

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Effects of ECT on Brain Structure: A Pilot Prospective Magnetic Resonance Imaging Study

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The authors describe a pilot prospective investigation of the effects of ECT on brain structure using magnetic resonance imaging (MRI). In nine patients with major depression, a course of ECT produced no acute changes in brain structure according to blind raters' assessments of cortical atrophy and global comparison of pre- and post-ECT studies. There were also no significant changes in the ventricle-brain ratios. Pre-ECT brain abnormalities were common in these patients yet were also unaffected by ECT. Future MRI studies of ECT should include more subjects and should address long-term changes and subtle brain abnormalities.

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Electroconvulsive therapy (ECT) is a safe and highly effective treatment for severe depression (1). However, its inherent relationship to seizures and its associated encephalopathic side effects have raised the theoretical concern that ECT may produce structural brain damage. A small number of radiologic studies using pneumoencephalography or computed axial tomography (CAT) have attempted to investigate this issue in humans. While the majority of the results have been negative, two studies (2, 3) have suggested an apparent association between ECT and cerebral atrophy as shown by brain CAT. Both studies were retrospective, however, and their results are limited by significant methodological difficulties (1).

With the introduction of magnetic resonance imaging (MRI) technology, more precise studies of brain morphology in vivo are now possible. Relative to CAT, brain MRI provides greater anatomic detail and more sensitivity to tissue injury (4, 5). As such, MRI is uniquely suited to the study of potential brain changes after ECT. In this paper we report the results of a pilot study using high-field-strength brain MRI to examine the potential effects of ECT on brain structure. To our knowledge, this is the first prospective investigation in humans of brain MRI before and after a course of ECT.

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METHOD

Subjects

The nine subjects were inpatients with *DSM-III* major depression (five with melancholia and one with psychotic features) who had been referred for ECT. All had been either refractory to or intolerant of previous trials of antidepressant medications; none had ever received ECT previously. There were five women and four men, and they had a mean age of 56 years (range, 43–78 years). The majority of the patients were medically healthy, but four (subjects 3, 4, 5, and 9) had histories of hypertension (subject 9 also had a remote history of coronary artery disease) and one (subject 1) had clinically inactive multiple sclerosis (6). The doses of any medications for these medical conditions were held constant throughout the course of ECT treatments. None of the patients received any psychotropic medications during the course of ECT. Informed consent was obtained for each of the research brain MRI scans.

ECT Technique

The ECT treatment techniques for the nine patients were similar. ECT was administered three mornings a week, on Monday, Wednesday, and Friday. The patients received anticholinergic premedication with glycopyrrolate, 0.002 mg/lb i.m., at least 30 minutes before the ECT. Anesthesia was induced with methohexital, 1 mg/kg i.v., followed by succinylcholine, 1 mg/kg i.v., to produce subtotal neuromuscular blockade. All patients were given 100% oxygen through a mask, and once they were apneic, their respirations were maintained at 20–25/minute with positive pressure ventilation by bag until spontaneous respirations returned. All patients were monitored with ECG and one-channel EEG.

The choice of stimulus electrode placement was made by the attending physician. For unilateral nondominant ECT, the d'Elia placement technique (7) was used. Four patients received unilateral nondominant ECT, and four received bilateral ECT. During the course of ECT the other patient was switched from unilateral to bilateral ECT because of a poor therapeutic response to the former. The total number of ECT treatments was determined by the attending physician; the average number was 7.2 (range, 5–11).

The ECT stimulus was delivered by a MECTA Model C (brief pulse) device to seven patients; the remaining two patients received sine wave (Medcraft) stimulation. For each ECT treatment, seizure duration was determined from the one-channel EEG on the basis of standard criteria (8). A "moderately suprathreshold" stimulus dosing strategy was employed: 1) parameters for each of the devices were chosen empirically to elicit seizures of at least 30 seconds' duration in the first ECT in over 80% of the cases, and 2) stepwise increases in stimulus intensity of at least 30% were employed in cases of brief or missed seizures or seizures of rapidly declining duration. No more than two restimulations were administered during any one treatment session.

Clinical Ratings

Clinical response to the course of ECT was evaluated on the basis of the 6-point Clinical Global Impression (CGI) severity scale (9), which was completed by the patient's clinical treatment team together with the ECT service. These consensus ratings were performed before the beginning of ECT (baseline) and again 2–3 days after completion of the course of ECT (follow-up), before continuation drug therapy was started. All ratings were made by raters blind to the results of the brain MRI studies.

The CGI determinations were supplemented by observer ratings of symptom severity, which were available as a result of the patients' participation in other research protocols; three patients received the Hamilton Rating Scale for Depression, and six patients received the Montgomery-Asberg Depression Rating Scale (10).

After each ECT treatment, the patients were assessed for recovery of pre-ECT orientation by trained nursing personnel using a standardized rating scale (11).

Brain MRI

Each subject received two brain MRI examinations—one at baseline and one 2–3 days after completion of the course of ECT (follow-up). All brain MRI studies were performed with a General Electric 1.5-tesla Signa system. For each study, spin-echo pulse sequences were used to generate both T_1-weighted (TR=500 msec, TE=20 msec) and T_2-weighted (TR=2000 msec, TE=40 and 80 msec) brain images. For both the T_1- and T_2-weighted images, a series of 5-mm thick sections with 2.5-mm interscan gaps was performed. The other technical parameters included a 128×256 pixels matrix, a field of view of 20 cm, and 2 excitations.

For six subjects the brain MRI scans were obtained in the standard axial imaging plane, which was parallel to the orbitomeatal baseline (0°). For the remaining three subjects (subjects 2, 3, and 7), the scans were obtained in the coronal imaging plane (perpendicular to the canthomeatal line) because of their participation in a separate research protocol.

To ensure the reproducibility of the scanning planes, head position was assessed and adjusted before each study with T_1-weighted sagittal images. The patient's head position was maintained throughout the scanning procedure with molded foam head supports and Velcro straps.

The brain MRI scans were analyzed by a board-certified neuroradiologist (W.T.D.) and a neurologist/psychiatrist (C.E.C.), both of whom were blind to the status (baseline or follow-up) and clinical interpretation of each study. Each set of scans was formally rated for evidence of changes in brain structure as defined by three variables—cortical atrophy score, ventricle-brain ratio (VBR), and pairwise global rating.

The cortical atrophy score was a rating of sulcal size irrespective of the patient's age and was determined with the 5-point rating scale of Largen et al. (12), which is shown in appendix 1. Predefined visual standards were established for each grade for comparison. The cortical atrophy score for each study was defined as the average of the scores of the two raters.

The VBR was determined for the six patients who received axial MRI scans by using a computer-assisted modification of the planimetric technique described by Weinberger et al. (3). A photograph of the MRI slice that included the widest portion of the bodies of the lateral ventricles was selected for measurement. The baseline and follow-up photographs from each of the six patients were then mixed together and analyzed in random order by a rater (C.E.C.) blind to the patients' names and treatment status (baseline or follow-up). The boundaries of the lateral ventricles and of the brain were traced with an electronic stylus, and the area of each was automatically calculated by a computer with specialized software. Each area was traced five times, and the mean value was used. The VBR was calculated by dividing the ventricular area by the brain area and multiplying by 100. To minimize the partial volume effect on ventricular area, we excluded from measurement any gray or partial-volume zones (3). A paired t test was used to assess the statistical significance of any change in VBR from baseline to follow-up.

The pairwise global rating consisted of a simultaneous comparison of the baseline and follow-up brain MRI studies, again with both raters blind to the treatment status (baseline or follow-up) and clinical interpretation of each study. The raters determined

whether there was a difference between the two studies (yes or no) and, if so, which study was most abnormal. The description of any abnormality was also recorded. The pairwise global rating supplemented the cortical atrophy score and allowed us to investigate whether a course of ECT might be associated acutely with other potential changes in brain structure, e.g., discrete lesions or changes in subcortical white matter, such as periventricular hyperintensity or deep white matter hyperintensity (4, 5).

The clinical interpretation of each MRI study by the attending neuroradiologist was also recorded and compared to the blind ratings. This interpretation always included a determination of whether any observed prominence of the cortical sulci was considered appropriate for the age of the patient.

RESULTS

All but one of the patients were thought by their attending physicians, the ward treatment teams, and the ECT service to have become euthymic or at least significantly improved (symptoms rated "none" to "mild" on the CGI scale) after the course of ECT (table 1). This clinical improvement was associated with parallel reductions in the depression scores. One patient (subject 6) failed to respond fully to a course of seven bilateral pulse ECTs.

The eight patients who responded to the course of ECT tolerated the treatments without any major adverse systemic or encephalopathic side effects. Specifically, these patients did not complain of persistent short-term memory disturbances, and the times for recovery of orientation after ECT (usually less than 1 hour) were well within the normal range for our unit. The exception was subject 6, the only nonresponder—she developed a marked delirium associated with diffuse background slowing of the EEG and focal slowing in the left temporal area. The delirium cleared within 5 days after the ECT was discontinued, at which time the patient appeared somewhat less depressed and was no longer suicidal.

All subjects were able to cooperate fully with both the baseline and follow-up brain imaging studies, the results of which are also summarized in table 1. According to the clinical interpretation of the attending neuroradiologist, six of the nine patients had abnormal MRI scans at baseline. The abnormalities consisted of cortical atrophy (N=5) and/or foci of periventricular and/or deep white matter hyperintensity (N=6). In subject 1, the periventricular and deep white matter lesions were felt to be consistent with her clinical history of multiple sclerosis (6); in the other five patients, the white matter abnormalities were interpreted as ischemic changes secondary to atherosclerosis of the medullary arteries (4, 5). After completion of the course of ECT, the scans of each patient were read clinically by the attending neuroradiologist (blind to the research) as unchanged. Specifically, none of the patients with previously normal MRI studies had developed any new abnormalities, and there were no changes in the studies of the patients with preexisting brain lesions.

The formal assessments of cortical atrophy, made by raters blind to baseline or follow-up status, indicated that five patients had at least mild (score≥2) cortical atrophy at baseline. These ratings agreed well with the clinical interpretations of the attending neuroradiologist. After completion of the course of ECT, the cortical atrophy ratings were unchanged. Again, none of the patients had any worsening of cortical atrophy (either focally or globally) after ECT, and none of the normal patients developed new atrophy.

For the six patients who received axial brain MRI scans, the mean±SD VBR before ECT was 8.95±3.57. The VBRs were in reasonable agreement with the qualitative clinical assessments of ventricle size made by the attending neuroradiologist. After the course of ECT the VBR was 8.97±3.30. There was no significant change in the VBRs over the course of the ECT treatments (paired t test; t=0.60, df=5, p=0.57).

The pairwise global rating of each patient's two sets of studies, also done by raters blind to baseline or follow-up status, revealed no difference between the baseline and follow-up scans. Specifically, there was no difference between the baseline and follow-up MRI studies with respect to cortical atrophy, ventricle size, periventricular or deep white matter hyperintensity, or any other potential changes.

DISCUSSION

Only a small number of previous radiologic studies have attempted to examine whether ECT produces structural brain damage. Results from investigations using pneumoencephalography have revealed no ECT-associated changes (1). Similarly, the results of the majority of brain CAT studies have been negative. Menken et al. (13) found no changes 3 hours after a single ECT session involving 10 seizures in a patient with recurrent unipolar depression. Johnstone et al. (14) found no relationship between enlarged lateral ventricles and previous ECT in 17 institutionalized schizophrenic patients. Dolan et al. (15) and Kolbjensson et al. (16) found no relationship in depressed patients between either ventricular enlargement or cortical atrophy and a previous history of ECT. Kendell and Pratt (17) found no abnormalities in seven unselected patients who had received "very large numbers" of ECTs, and both Nasrallah et al. (18) and Pearlson et al. (19) found no difference in the number of lifetime ECTs between manic-depressive patients with and without lateral ventricular enlargement.

Two studies, both retrospective, have suggested a relationship between ECT and brain changes shown by CAT. Calloway et al. (2) reported an association in elderly depressed patients between frontal lobe atrophy (sulcal widening assessed by a radiologist and a

retrospectively obtained history of ECT. Frontal lobe atrophy was found in 15 of 22 patients with histories of ECT, and its presence correlated with the number of previous treatments. This report remains controversial, however (20), in that frontal atrophy was also seen in four of 15 patients who had never received ECT. Furthermore, the ECT and non-ECT groups in that study had comparable global atrophy scores and ratings of lateral ventricular size. In a group of chronic schizophrenic patients with enlarged lateral ventricles, Weinberger et al. (3) found that those patients who had received ECT had higher VBRs than those who had not received ECT. However, over half of their patients with ventricular enlargement had never received ECT.

The significance of those two reports remains unclear given their retrospective methods. While ECT may have caused cerebral atrophy, alternate explanations are equally plausible. For example, there may exist a subgroup of depressed patients who are likely, for whatever reasons, to develop cerebral atrophy. Perhaps because of these brain changes, such patients might be refractory to medications and thus referred for ECT, or they might be relatively unresponsive to treatment and hence require more ECTs than patients without brain changes (2, 5). Clearly, only prospective studies can address these issues.

In the present investigation, a more sensitive imaging technique, MRI, was used to investigate prospectively whether a conventional course of ECT is associated with acute changes in brain structure. In our nine patients with depression, ECT produced no change in brain structure shown by MRI according to formal ratings of cortical atrophy, quantitative determinations of ventricle size based on the VBR, and a global comparison of baseline and follow-up studies. For all assessments, the raters were blind to the pre- versus post-ECT treatment status of each study, thereby greatly reducing the likelihood of biased evaluations. Furthermore, in every case the blinded clinical interpretation of the MRI scans by the attending neuroradiologist revealed no change between the baseline and follow-up studies.

In four of six patients, there was a nonsignificant trend toward higher VBRs after the course of ECT. Whether this observation actually reflects a change in brain structure or is an artefact of technique remains unclear, however, given that we have observed rather wide variability in the VBRs of serial MRI studies for the same patient. This variability can be attributed to subtle differences in head tilt, which are very difficult (if not impossible) to eliminate. In addition, the validity of the VBR as a measure of cortical atrophy has recently been questioned (21). A more valid and reliable measure of ventricle size might be quantitative volumetric assessment from contiguous *coronal* sections through the entire ventricular system, a technique that we are currently exploring.

Our results suggest that the acute encephalopathic side effects of ECT are not associated with gross anatomic brain damage. We observed no acute structural brain changes even in those five patients who had received bilateral ECT, the type of ECT most commonly associated with the severest degree of acute confusion and disturbances of short-term memory. Indeed, in the one patient who developed a marked delirium (subject 6), the brain MRI scan remained unchanged even when the EEG had become abnormal. Since our follow-up scans were performed 2–3 days after the last ECT, however, it would have been possible to miss structural brain changes that could theoretically have taken longer to evolve. For this reason, long-term follow-up imaging studies are needed and are in progress in our laboratories.

We observed a surprisingly high occurrence of preexisting brain abnormalities in our patients. Of the nine subjects, six had evidence on baseline MRI studies of structural brain disease. One patient (subject 1) had laboratory-supported definite multiple sclerosis. As previously reported (6), she was successfully treated with ECT without any adverse neurologic effects or any changes in the demyelinating white matter lesions

TABLE 1. Effect of ECT on Clinical State and Brain MRI Results of Nine Patients

Patient	Age (years)	Sex	Number and Type of ECTs	CGI Score	
				Baseline	Follow-Up[a]
1	43	F	6 unilateral pulse	6	1
2	46	M	8 unilateral pulse	5	3
3	55	F	8 unilateral pulse	5	2
4	59	M	7 unilateral pulse, then 4 bilateral pulse	5	2
5	60	F	8 bilateral pulse	5	2
6	72	F	7 bilateral pulse	5	4
7	42	F	5 bilateral sine wave	6	2
8	48	M	6 bilateral sine wave	6	1
9	78	M	6 unilateral pulse	5	2

[a]Follow-up data were obtained 2–3 days after completion of the course of ECT.
[b]Patients 1–6 assessed with the Montgomery-Asberg Depression Rating Scale (10); patients 7–9 assessed with the Hamilton Rating Scale for Depression.
[c]From 5-point rating scale of Largen et al. (appendix 1).
[d]Comparison of baseline and follow-up MRI studies.
[e]PVH=periventricular hyperintensity; DWMH=deep white matter hyperintensity.

TABLE 1
(continued)

Depression Score[b]		Results of Brain MRI						
		Cortical Atrophy Score[c]		VBR		Pairwise Global Rating[d]	Clinical Interpretation[e]	
Baseline	Follow-Up[a]	Baseline	Follow-Up[a]	Baseline	Follow-Up[a]		Baseline	Follow-Up
42	5	0.0	0.0	7.7	7.3	No difference	Scattered foci of PVH and DWMH, consistent with clinical history of multiple sclerosis	No change
38	18	1.0	1.0	—	—	No difference	Normal	No change
36	2	3.5	3.5	—	—	No difference	Moderate to severe cortical atrophy, with severe frontal atrophy; mild ventricular enlargement; scattered foci of PVH and DWMH	No change
47	17	3.0	3.0	10.8	13.0	No difference	Moderate cortical atrophy with mild lateral ventricular enlargement, left greater than right; scattered foci of PVH	No change
42	20	2.0	2.0	5.4	6.0	No difference	Mild cortical atrophy; scattered foci of PVH and DWMH	No change
45	30	3.0	3.0	9.2	9.7	No difference	Moderate cortical atrophy with mild ventricular enlargement; multiple foci of PVH and DWMH, similar foci of increased T_2 signal in basal ganglia and brain stem consistent with lacunar infarctions	No change
27	18	1.0	1.0	—	—	No difference	Normal	No change
20	10	0.0	0.0	4.6	5.3	No difference	Normal	No change
26	6	4.0	4.0	14.2	12.5	No difference	Severe cortical atrophy with moderate lateral ventricular enlargement; scattered foci of PVH and DWMH	No change

visualized on T_2-weighted MRI scans. An additional five patients had combinations of cortical atrophy (of varying severity) and high-signal intensity lesions of the subcortical white and gray matter. These changes were felt to be most consistent with subcortical arteriosclerotic encephalopathy, an increasingly recognized form of atherosclerotic cerebrovascular disease characterized pathologically by discrete lacunar infarctions and loss of the white matter with gliosis (4, 5). This syndrome is associated with vascular risk factors and is felt to result from atherosclerotic disease of the small, deep, penetrating arteries that supply subcortical brain regions (4, 5). Although we observed no acute worsening of these subcortical lesions in our patients after ECT, future studies should provide formal assessments of subcortical as well as cortical structures.

Although the relationship of these brain abnormalities to the clinical depression in our patients remains unclear, we have reported that affective disturbances are common in patients with subcortical arteriosclerotic encephalopathy and that ECT may be an effective form of therapy (4, 5). In the present study, four of the five patients with cortical atrophy and subcortical arteriosclerotic encephalopathy showed a prompt clinical improvement after ECT. The one nonresponder showed only partial clinical improvement before her treatment course was interrupted by a delirium.

It has been suggested that organic brain disease may increase the risk of ECT-related cognitive deficits. While the risk of encephalopathy from ECT in patients with cortical atrophy and subcortical arteriosclerotic encephalopathy is unknown, all of our responders tolerated the course of ECT without any prolonged disorientation or complaints of disturbed short-term memory. In addition, follow-up MRI studies revealed no acute changes in the actual brain lesions themselves after the course of ECT. Still, further work is required to determine the extent to which varying degrees of brain impairment influence the course of affective disorder and its response to ECT and drug therapy. Since some patients with subcortical arteriosclerotic encephalopathy may also go on to develop cognitive dysfunction, the long-term effects of ECT and drug

therapy on this disease process will need to be carefully studied.

In summary, we observed no acute structural brain changes in nine patients with depression who were studied with brain MRI before and after a standard course of ECT. Furthermore, patients with preexisting cortical and subcortical structural brain disease showed no worsening of their lesions as visualized on the MRI scans. Still, these initial observations need to be confirmed in a larger number of subjects with techniques that will quantitate even subtle brain changes which otherwise might not be detected by qualitative clinical assessments. Future studies should also include patients with histories of previous ECT (to evaluate any potential cumulative effects) and should involve long-term follow-up studies including both subjective and objective measures of memory function.

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APPENDIX 1. Cortical Atrophy Rating Scale of Largen et al. (12) Modified for MRI

0=(N) None	No atrophy of cortex and no abnormally wide sulci. Sulci not very abundant. In uppermost cut an occasional prominent sulcus may be seen.
1=(Q) Slight, Questionable	Edges of cortex slightly atrophied, and/or slight widening in one or two sulci. No evidence of sulcal widening or atrophy on lower cuts.
2=(M) Mild	Definite atrophy which is not very extensive, and sulcal widening in several sulci. Some evidence of atrophy and/or widened sulci in lower cuts.
3=(MO) Moderate	Definite atrophy of cortex which extends in a distance from edges. Atrophy does not engulf entire brain area (e.g., entire frontal brain), and marked atrophy is often limited to one area of the brain. Marked sulcal widening and/or enlarged sulci characteristic of much of brain. Interhemispheric fissure is usually widened.
4=(S) Severe	Large areas of atrophy accompanied by general sulcal widening of most sulci. Atrophy and sulcal widening are prominent in lower cuts. Brain looks definitely shrunken. Interhemispheric fissure widened.

The Dexamethasone Suppression Index: Enhancement of DST Diagnostic Utility for Depression by Expressing Serum Cortisol as a Function of Serum Dexamethasone

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The authors sought to determine whether the performance of the dexamethasone suppression test (DST) could be enhanced by expressing cortisol as a function of dexamethasone. Because cortisol concentration is a function of the reciprocal of dexamethasone concentration, this relationship was approximated by calculating the product of cortisol and dexamethasone as a dexamethasone suppression index. Preliminary assessment of test performance measures (sensitivity, specificity, and predictive power) showed that use of the dexamethasone suppression index was an improvement over the use of cortisol levels alone. Factoring dexamethasone levels into post-dexamethasone cortisol level measures may enhance the utility of neuroendocrine assessment in psychiatry.
(Am J Psychiatry 1988; 145:707–711)

Following the landmark publication in 1981 by Carroll et al. (1) reporting results for a standardized 1-mg dexamethasone suppression test (DST) to support a diagnosis of depressive disorder, a virtual explosion in clinical psychiatric research has occurred using this relatively simple neuroendocrine test (2). Reviews of this expanding literature (2–7) found an overall sensitivity of 45% (range=30%–60%) and an overall specificity of 75% (range=50%–95%).

Because methods for assessment of dexamethasone levels were not readily available until recently, interindividual variations in the absorption and pharmacokinetics of this synthetic glucocorticoid analogue were not adequately assessed. Since the effectiveness of feedback suppression of the hypothalamic-pituitary-adrenal (HPA) axis by dexamethasone is a function of the level of dexamethasone, it would be reasonable to postulate that the sensitivity and specificity of the test would be improved if cortisol levels determined after administration of dexamethasone were expressed as a function of the blood dexamethasone levels rather than as an absolute concentration. That this is true for the diagnosis of Cushing's disease (the disorder in which the value of a DST was initially described) was established by Meikle (8). Also, other investigators, including ourselves, have shown that DST nonsuppression in psychiatric patients is associated with low plasma dexamethasone, and DST suppression is associated with higher dexamethasone levels (6, 9–13). In some studies (9–13) up to a 100-fold variation in dexamethasone levels was observed in the 9–15 hours following the administration of 1 mg of dexamethasone.

In this study, we sought to determine whether measurement of cortisol suppression as a function of dexamethasone level would improve the performance of the DST. This hypothesis was suggested from earlier work (9). According to the underlying negative feedback mechanism of dexamethasone suppression in the HPA axis, it was postulated that cortisol levels are a negative function of achieved dexamethasone levels. Because curve-fitting analysis follows an inverse curvilinear function (14, 15), as a first approximation we tested the hypothesis that the use of a simplified expression of this function as the arithmetical product of dexamethasone and cortisol levels would enhance the utility of the DST. We followed the general equation for an inverse curvilinear function $(Y+a=[K+b]/[X+c])$, where Y is the cortisol level, X is the dexamethasone level, and K represents the derived dexamethasone suppression index. The arithmetic product, which for convenience we call the dexamethasone suppression index, has been reported in an abstract (14). Carr et al. (15) used the same concept for studies of the DST in depression. The dexamethasone index is expressed as $[\text{nmol/liter}]^2$.

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METHOD

Consecutively admitted patients were screened for inclusion in the study and underwent medical and neurological examination. Normal volunteers were screened for medical and psychiatric illnesses by interview. Only those patients and normal volunteers who met strict criteria for a technically valid DST (2) were considered for study.

To determine the presence or absence of depression we used the Hamilton Rating Scale for Depression. Patients in the depressed subgroup had scores of 20 or more; patients in the nondepressed subgroup had scores under 15. All patients were competent and gave consent for study. All volunteers also provided informed consent. Diagnoses were established by using *DSM-III-R*, clinical interviews, and detailed psychiatric histories. Particular attention was taken to exclude any patient whose diagnosis was questionable or who demonstrated a mixed diagnostic picture. All patients had been drug free for no less than 7 days before the study began.

Cortisol and dexamethasone levels were determined by using standardized radioimmunoassays previously described (9). The dexamethasone radioimmunoassay has intra- and interassay coefficients of variation of 8% and 15%, respectively, with 50% displacement of labeled trace attained at 11 pg. Cross-reactivity with cortisol and corticosterone with this assay is less than 0.02%.

RESULTS

Sixteen hospitalized patients with *DSM-III-R* major depression, nine hospitalized control patients with psychiatric diagnoses other than major depression, and eight nonhospitalized volunteer control subjects were given the standard DST overnight test, which included simultaneous measurement of both cortisol and dexamethasone (table 1). All of the patients and volunteer control subjects were men, and the two control groups were matched in age to the depressed patients. The patients with major depression had a mean age of 45 years (range=35–61), the psychiatric control patients had a mean age of 40 (range=31–55), and the nonpsychiatric control subjects had a mean age of 35 (range=27–40). The mean dexamethasone levels in the depressed, psychiatric control, and normal control groups were similar at 8:00 a.m. and 12:00 noon (see table 1). Among all subjects studied, however, there was a 17-fold variation in dexamethasone levels at 8:00 a.m., a 43-fold variation at 12:00 noon, and a 20-fold variation at 4:00 p.m. (see table 1).

The depressed patients had a significantly higher mean 8:00 a.m. dexamethasone suppression index than either the psychiatric control patients ($t=4.29$, $df=23$, $p<0.001$) or the normal control subjects ($t=4.04$, $df=22$, $p<0.001$) (see table 1). No difference was found between psychiatric control patients and normal control subjects at 8:00 a.m. ($t=0.68$, $df=15$, n.s.). At 12:00 noon, the depressed patients again demonstrated a significantly higher mean dexamethasone suppression index than either psychiatric control patients ($t=3.47$, $df=23$, $p<0.005$) or normal control subjects ($t=3.98$, $df=22$, $p<0.001$). There was no difference between psychiatric control patients and normal control subjects when 8:00 a.m. and 12:00 noon data were compared. Although insufficient data were available to calculate 4:00 p.m. values in both control groups studied, according to standard DST criteria (postdexamethasone cortisol level greater than 138 nmol/liter), seven (43.8%) of the 16 depressed patients were DST positive (see table 1).

To assess whether the sensitivity of the HPA axis to suppression by dexamethasone was related to the time of day tested and whether it was a function of psychiatric diagnosis, we compared the dexamethasone suppression index in depressed and control groups across the 8:00 a.m. and 12:00 noon time points (see table 1). In the depressed patients there was no significant difference between 8:00 a.m. and 12:00 noon in the mean dexamethasone suppression index ($t=0.82$, $df=15$, $p>0.2$). In contrast, the psychiatric control patients showed a moderately significant difference between 8:00 a.m. and 12:00 noon ($t=2.81$, $df=16$, $p<0.05$) and the normal control subjects had a highly significant difference in dexamethasone suppression index between these same time points ($t=3.11$, $df=14$, $p<0.01$) (see table 1).

To evaluate the utility of simplifying the DST as currently performed by employing a single 8:00 a.m. blood test, we compared the sensitivity and specificity of the 8:00 a.m. cortisol level with those for the dexamethasone suppression index for four values of cortisol and four values of the dexamethasone suppression index (see table 2). In this analysis, we combined the psychiatric control patients and the normal control subjects to determine specificity. The data show that at a cortisol criterion of 60 nmol/liter at 8:00 a.m., the specificity achieved was 100% and the sensitivity was 31% (see table 2). In comparison, at a criterion level of 400 $[\text{nmol/liter}]^2$, the specificity was 100% and the sensitivity was 69%. Figure 1 plots 8:00 a.m. cortisol and dexamethasone levels in all patients studied with the cutoff criterion of 400 $[\text{nmol/liter}]^2$. This figure shows the separation achieved between depressed subjects and control subjects by using a product of cortisol and dexamethasone.

DISCUSSION

In this study we found that the expression of cortisol levels as a function of dexamethasone levels in the DST enhances its utility for the diagnosis of depression. Carr et al. (15) recently reported similar findings. We derived the dexamethasone suppression index as a rough approximation of the relationship between cortisol level and dexamethasone levels following the

TABLE 1. Cortisol and Dexamethasone Levels and Dexamethasone Suppression Index of Inpatients With Major Depression or Other Psychiatric Diagnoses and of Eight Normal Volunteers

Subject	Cortisol (nmol/liter)			Dexamethasone (nmol/liter)			Dexamethasone Suppression Index ([nmol/liter]^2)		
	8:00 a.m.	12:00 noon	4:00 p.m.	8:00 a.m.	12:00 noon	4:00 p.m.	8:00 a.m.	12:00 noon	4:00 p.m.
Patients with major depression (N=16)									
1	50	58	41	9.25	3.00	0.25	463	174	10
2	17	25	14	6.75	4.50	0.25	115	113	4
3	41	289	305	1.25	0.25	0.25	51	72	76
4	17	25	19	15.25	8.50	4.75	259	213	90
5	14	110	94	21.75	7.50	3.50	305	825	329
6	47	58	17	10.75	6.75	5.00	505	392	85
7	36	47	11	11.00	4.75	2.75	396	223	30
8	41	36	8	9.50	5.00	2.25	390	180	18
9	105	99	245	11.50	5.75	4.00	1,208	569	980
10	102	113	305	8.25	2.50	1.75	842	283	534
11	39	30	85	12.00	4.75	1.75	468	143	149
12	83	66	215	11.25	5.50	2.50	934	363	538
13	36	173	176	16.50	5.75	3.75	594	995	660
14	41	47	121	17.75	5.50	1.50	728	259	182
15	116	264	—	8.25	4.00	—	953	1,506	—
16	140	162	—	6.75	3.25	—	947	527	—
Mean	57.8	100.1	118.3	11.1	4.80	2.30	572.4	399.2	263.2
SD	38.8	82.7	111.2	4.9	2.00	1.70	332.7	312.7	302.1
Patients with other diagnoses (N=9)[a]									
17	11	11	6	7.25	5.00	2.75	80	55	17
18	11	11	8	12.00	7.25	3.75	132	80	30
19	8	8	—	20.00	13.00	—	163	107	—
20	30	41	—	6.00	4.50	—	182	186	—
21	10	10	—	18.50	10.75	—	185	108	—
22	17	14	—	6.25	6.25	—	103	86	—
23	19	17	14	11.00	6.00	2.75	209	102	39
24	36	28	28	8.25	7.00	4.50	297	196	126
25	25	22	—	12.50	4.50	—	309	99	—
Mean	18.6	18.0	—	11.30	7.10	—	184.4	113.2	—
SD	9.9	10.8	—	5.10	2.90	—	78.7	47.1	—
Normal volunteers (N=8)									
26	14	11	11	9.00	4.00	3.25	124	44	—
27	50	8	11	8.00	5.00	2.50	398	41	—
28	17	19	—	6.75	5.75	—	115	109	—
29	19	19	—	7.50	5.75	—	143	109	—
30	14	11	—	11.50	5.50	—	161	61	—
31	17	14	—	14.50	8.25	—	247	116	—
32	17	11	—	9.50	5.00	—	162	55	—
33	22	11	—	10.50	5.00	—	231	55	—
Mean	21.3	13.0	—	9.70	5.50	—	197	74	—
SD	11.9	4.0	—	2.50	1.20	—	93	32	—

[a]Patients 17–22 had diagnoses of schizophrenia, patient 23, antisocial personality disorder, patient 24, delusional disorder, and patient 25, impulse control disorder.

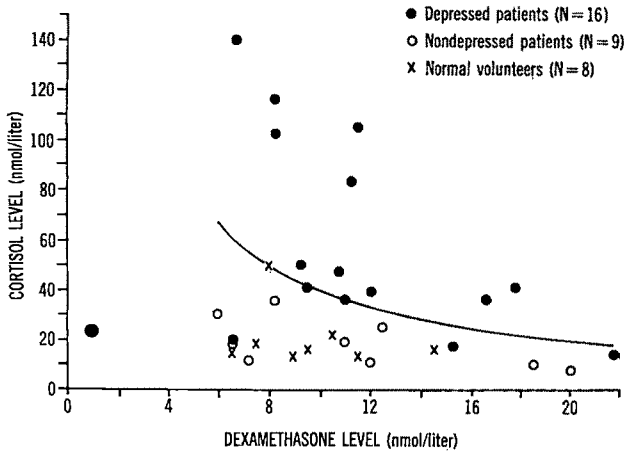
general equation for an inverse curvilinear function. This relationship has been demonstrated to be applicable in the relationship of dexamethasone to cortisol in man (8, 14, 15). Carr et al. (15) did not present dexamethasone suppression index data for depressed patients versus control subjects. When our 8:00 a.m. dexamethasone suppression index data for depressed and psychiatric control patients were pooled, we found a product of 433 [nmol/liter]^2 for the 25 patients, which is similar to that published by Carr, who found a value of 430 [nmol/liter]^2 at 8:00 a.m. (15).

The use of the dexamethasone suppression index reinforces several previous conclusions about pituitary-adrenal function in depression. We found that the dexamethasone suppression index was significantly higher at 8:00 a.m. and 12:00 noon in depressed patients than it was in both psychiatric control patients and normal control subjects, indicating that there is a resistance to suppression even though there is variation in dexamethasone levels. There was no significant difference in suppressibility between 8:00 a.m. and 12:00 noon in the depressed group, but there was a significant difference in the dexamethasone suppression index between these two time points in psychiatric control patients and normal control subjects. This same shift of the dexamethasone suppression index between 8:00 a.m. and 4:00 p.m. was also reported by Carr et al. (15) for pooled data. Our data are consist-

TABLE 2. Sensitivity, Specificity, and Positive Predictive Power of 8:00 a.m. Cortisol Levels and the Dexamethasone Suppression Index in Separating 16 Inpatients With Major Depression From 17 Control Subjects

Criterion Used to Diagnose Depression	Sensitivity (%)	Specificity (%)	Positive Predictive Power (%)
Cortisol			
35 nmol/liter	81	88	87
40 nmol/liter	63	94	91
50 nmol/liter	38	94	86
60 nmol/liter	31	100	100
Dexamethasone suppression index			
250 [nmol/liter]^2	88	82	82
300 [nmol/liter]^2	81	88	87
350 [nmol/liter]^2	75	94	92
400 [nmol/liter]^2	69	100	100

FIGURE 1. Relationship of 8:00 a.m. Dexamethasone and Cortisol Levels of Inpatients With Major Depression or Other Psychiatric Disorders and of Normal Volunteers[a]



[a]The curved line shows the dexamethasone suppression index value of 400 [nmol/liter]^2, which, when used as a criterion value to separate depressed patients from the two control groups, yielded a sensitivity of 69% and a specificity of 100%.

ent with the observation that, in addition to the hypersecretion of cortisol evident in depressed patients, the circadian rhythm of the HPA axis among depressed patients is blunted as compared with that of control populations (16). Furthermore, in normal subjects there is a time-dominated sensitivity to suppression (17, 18).

Resistance to suppression by dexamethasone has been taken to indicate that the HPA axis operates at a higher setpoint in patients with depression than in normal subjects. Although the use of the dexamethasone suppression index suggests that there is a true resistance to suppression in depression, there may be an abnormality in dexamethasone kinetics in certain psychiatric illnesses. Depressed patient 3 clearly demonstrated a dramatically low dexamethasone level (see table 1 and figure 1), showing that a "true" dexamethasone suppression index would need to be repeated with a higher dose of dexamethasone in order to achieve an adequate dexamethasone level. Holsboer et al. (19) found that DST-positive depressed patients had a significantly shorter half-life of dexamethasone (160 minutes) than DST-negative patients (422 minutes); this led them to postulate that DST-positive depressed patients may have an accelerated metabolism of dexamethasone rather than decreased absorption. If a subset of DST-positive depressed patients also metabolize dexamethasone rapidly, it may be because they have chronic pronounced hypercortisolemia, which has been shown to lead to a decreased half-life of cortisol (17, 18). It is possible that the hypercortisolemia in this subset of depressed patients leads to positive DST results because of faster dexamethasone metabolism resulting in lower dexamethasone levels at certain times as well as because of the underlying centrally driven hypercortisolemia.

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Psychiatric Disorder and Limitations in Physical Functioning in a Sample of the Los Angeles General Population

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The authors examined relationships between psychiatric disorder and perceived general health and physical functioning from data obtained from interviews with 2,554 non-Hispanic whites and Mexican-Americans in Los Angeles. Persons with recent psychiatric disorders perceived their general health as poorer and had more limitations in physical functioning than persons without such disorders, even when the analyses controlled for chronic medical conditions and demographic factors. Affective and anxiety disorders were independently associated with both acute and chronic limitations in physical functioning. The associations of recent psychiatric disorder and of chronic medical condition with acute activity restrictions were similar in magnitude.

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Physical functioning refers to the ability of an individual to carry out daily activities such as dressing and bathing, the capacity to perform physical tasks such as exercise, and the extent of any restriction in physical activity, such as partial or complete days of rest in bed (hereinafter called "bed days") (1–4). The physical functioning of persons with psychiatric disorders is of clinical interest for several reasons. First, grave disability is a common indication for inpatient psychiatric admission. Second, physical limitations may be inappropriately attributed to medical rather than psychiatric problems (and vice versa) by patients and health care providers. Third, limitations in physical functioning affect patients' choice of provider (general medical versus mental health specialist) of mental health care (5).

Measures of physical functioning, such as disability days, are commonly used as indicators of need for services in health policy studies and in planning or allocating services (3, 6). These measures are assumed to reflect physical rather than psychiatric problems. Data on the relation of perceived general health and functional status to psychiatric disorder would be useful in determining the extent to which these measures indicate a need for mental health services.

Previous studies of physical functioning and mental illness have focused on either chronic mental patients (7) or general psychological distress in community samples (8–12) rather than on persons with psychiatric disorders. These studies found significant associations between psychological distress or depressed mood and the number of restricted activity days (9), bed/disability days (10, 11), and work absenteeism (11, 12). An especially important limitation of these studies was the failure to control for the effects of chronic medical conditions on physical functioning and general health status. In previous studies limitations in physical functioning attributed to psychological status could have been partly due to the confounding effects of (unmeasured) chronic medical conditions.

In this study we examined the associations of psychiatric disorders with perceptions of general health and indicators of physical functioning while controlling for the presence or absence of chronic medical conditions. We hypothesized that persons with either a psychiatric disorder or a chronic medical illness would be significantly more likely to view themselves as in poor general health and that both psychiatric disorders and chronic medical conditions would be independently associated with limitations in physical functioning.

METHOD

The National Institute of Mental Health (NIMH) Epidemiologic Catchment Area Program is a multisite general population survey of the epidemiology of psychiatric disorders and use of health services (13, 14). In the Los Angeles part of the project, staged probability samples of household residents from two mental health catchment areas (East Los Angeles and Venice/Culver City) were drawn. Approximately 50% of the respondents were of Hispanic origin (mostly Mexican-American) (15). For each household, one adult was randomly selected to participate in a series

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of face-to-face interviews. The first wave of interviews was completed in 1982–1983. The response rate was 68% (N=3,132). This paper reports data on all Mexican-Americans and non-Hispanic whites in the sample (N=2,554). We excluded respondents from other ethnic groups, which were represented in small numbers, to allow meaningful control for ethnicity in the analyses.

Data on psychiatric disorders were obtained with the NIMH Diagnostic Interview Schedule (16), a structured interview administered by laypersons that yields diagnoses according to *DSM-III* criteria. A Spanish-language version of this instrument was developed specifically for this study (17, 18). We developed indicator variables for the presence of any psychiatric disorder, any affective disorder, any substance abuse disorder, and any anxiety disorder, as well as for each specific psychiatric disorder for the 6 months before interview (i.e., a recent disorder).

Our measure of chronic medical disease is a 15-item battery similar to items in the Hispanic Health and Nutrition Examination Survey (HANES) (19). It elicits data on presence or absence of eight groups of medical conditions and whether the respondent is under care for each condition: chronic lung disease (emphysema, asthma, or other chronic lung disease), diabetes mellitus, heart disease, hypertension, arthritis, physical handicap (amputation, paralysis, birth defect, deafness, or blindness), cancer, and stroke and other neurological conditions. We defined a recent (i.e., active) medical condition as one that was present or for which the respondent was under care at the time of the interview.

The interview included one item assessing perceived general health status that was used in the Rand health insurance experiment (20) and other health policy studies. The respondents rated their health as poor, fair, good, or excellent. The interview included a six-item measure of chronic restrictions in daily activities or job functioning due to physical health problems that was similar to items from the Hispanic HANES (19). We constructed an indicator variable for any chronic limitation in physical or job functioning. In addition, two items assessed the number of days of restricted activity and bed days due to physical illness in the 2 weeks before interview. Such items largely measure acute physical limitations. The interview elicited data on age, job status (scored by the Nam-Powers job status scale) (21), education, sex, marital status, and ethnicity (Mexican-American or non-Hispanic white).

We used cross-tabulations to determine the prevalence of poor health or poor functioning, according to each measure we have described, as a function of a recent psychiatric disorder and/or a chronic medical condition. Each of these estimates was sex- and age-adjusted, with the total analytic sample used as the reference group. To adjust for multiple statistical comparisons, we used the 0.005 level of significance for testing the association of any psychiatric disorder and/or chronic medical condition with functioning and the 0.001 level for testing the association of specific psychiatric disorders with functioning. We estimated multiple regression models to examine the association of recent psychiatric disorder with physical functioning and perceived general health, controlling for any chronic medical condition and demographic factors.

Data were weighted to adjust for differential probability of selection within households and across the two catchment areas. For the cross-tabulations, significance tests and standard errors were corrected by using the SESUDAAN program (22). For the logistic regressions, we estimated correction factors from a linear model (23) and applied these to the chi-square statistics for the significance of each logistic regression coefficient. Because the correction for the regression equations is an overcorrection, we simply used the 0.05 level for testing whether each coefficient differed from zero.

RESULTS

In the 6 months before interview, 54% (N=1,377) of the respondents had neither a psychiatric disorder nor a chronic medical condition, 13% (N=336) had a psychiatric disorder but no medical condition, 26% (N=656) had a medical condition but not a psychiatric disorder, and 7% (N=185) had both types of problems (see table 1).

Relative to respondents with neither type of health problem, the mean age was significantly lower for persons with psychiatric disorder alone ($t=4.43$, $df=1,711$, $p<0.001$) and significantly greater for those who had a medical condition with a psychiatric disorder ($t=7.76$, $df=1,560$, $p<0.001$) or without a psychiatric disorder ($t=19.0$, $df=2,031$, $p<0.001$). Persons with one or both types of problem were significantly less likely to be employed than those without either type of problem (range of t values from $t=2.63$, $df=1,711$, to $t=9.55$, $df=2,021$; each $p<0.01$). None of the other demographic differences between disease groups presented in table 1 was significant after adjustments for age, sex, and employment status (data not shown).

As shown in table 2, the percentage of persons with poor or fair perceived general health was greater (by 66%–253%) for persons with a recent psychiatric disorder and/or a chronic medical condition than for persons with neither type of health problem (range of t values from $t=3.60$, $df=1,711$, to $t=7.62$, $df=2,031$; each $p<0.001$). The prevalence of poor or fair general health was 32% greater for those with both types of disorder than for those with a chronic medical condition alone ($t=2.13$, $df=839$, $p<0.05$) and 61% greater for the latter group than for those with a psychiatric disorder alone ($t=3.94$, $df=990$, $p<0.001$).

Persons with a recent psychiatric disorder and/or a chronic medical condition had a significantly higher prevalence (by 139%–868%) of a chronic activity

TABLE 1. Demographic Characteristics of 2,554 Persons With and Without Recent Chronic Medical Illness and Psychiatric Disorder

	Respondents Without a Chronic Medical Condition				Respondents With a Chronic Medical Condition			
	Without Psychiatric Disorder (N=1,377)		With Psychiatric Disorder (N=336)		Without Psychiatric Disorder (N=656)		With Psychiatric Disorder (N=185)	
Characteristic	%	SE	%	SE	%	SE	%	SE
Female	47.7	1.5	50.2	3.4	54.1[a]	2.2	59.2[a]	3.7
Mexican-American	54.4	1.7	54.2	2.8	44.2[a]	2.1	48.6	4.1
Married	57.0	1.3	46.4[a]	3.0	57.3	2.2	54.0	4.4
Employed	72.8	1.0	64.0[a]	3.2	47.1[a]	2.5	46.2[a]	4.2
Age≥40 years	35.0	0.4	31.9[a]	0.6	52.1[a]	0.8	46.3[a]	1.4
High job status	46.7	0.9	45.2	1.5	43.6[a]	1.0	46.4	2.5

[a]Significantly different (t>1.96, df≥1,560, p<.05) from the percentage for persons with neither a psychiatric disorder nor a chronic medical condition (same row).

TABLE 2. Sex- and Age-Adjusted Prevalence of Functional Limitations and Poor or Fair Perceived General Health in 2,554 Persons With and Without Recent Chronic Medical Illness and Psychiatric Disorder

	Respondents Without a Chronic Medical Condition				Respondents With a Chronic Medical Condition			
	Without Psychiatric Disorder (N=1,377)		With Psychiatric Disorder (N=336)		Without Psychiatric Disorder (N=656)		With Psychiatric Disorder (N=185)	
Variable	%	SE	%	SE	%	SE	%	SE
Any chronic activity restriction	4.1	0.7	9.8[a]	1.8	21.0[a]	2.0	39.7[a]	3.8
Any restricted activity day in preceding 2 weeks	7.2	0.8	15.5[a]	2.2	14.0[a]	1.3	26.7[a]	3.9
Any bed days in preceding 2 weeks	4.8	0.6	10.2	2.0	6.4	1.0	17.9[a]	3.1
Poor or fair perceived general health	12.5	1.1	20.7[a]	2.0	33.3[a]	2.5	44.1[a]	4.4

[a]Significantly different (t>2.81, df≥1,560, p<0.005) from the percentage for persons with neither a psychiatric disorder nor a chronic medical condition (same row).

restriction than those with neither type of health problem (range of t values from t=2.95, df=1,711, to t=9.13, df=1,560; each p<0.001). Further, persons with either or both types of problem were significantly more likely (by 94%–271%) to have had a recent restricted activity day than persons with neither health problem (range of t values from t=3.55, df=1,711, to t=4.90, df=1,560; each p<0.001). The percentage of persons with any restricted activity day was significantly higher for those with both types of disorder than for those with either type of disorder alone (t=3.10, df=839, p<0.005, and t=2.50, df=519, p<0.01). In addition, persons with both psychiatric and medical problems were significantly more likely than those with neither type of problem to have had a bed day in the previous 2 weeks (t=4.15, df=1,560, p<0.005). Persons with a psychiatric disorder alone were somewhat more likely than persons with neither type of problem to have had a recent bed day, but the difference was significant only at the 0.01 level (t=2.58, df=1,711, p<0.01). Persons with a medical condition alone did not have a significantly greater likelihood of having had a bed day in the previous 2 weeks (table 2).

After correction for multiple comparisons and adjustment for sex and age, persons with major depression, dysthymia, alcohol use disorders, and anxiety disorders were significantly more likely (by 64%–162%) to report being in poor or fair general health than persons with no psychiatric disorder (range of t values from t=3.19, df=2,232, to t=6.16, df=2,121; each p<0.001) (see table 3). The same psychiatric disorders were significantly associated with any chronic limitation in daily activities or job performance (range of t values from t=4.16, df=2,232, to t=8.11, df=2,121; each p<0.001). The percentage with any restricted activity days in the preceding 2 weeks was significantly higher (by 171%–216%) for persons with major depression (t=4.42, df=2,121, p<0.001), dysthymia (t=4.23, df=2,153, p<0.001),

TABLE 3. Sex- and Age-Adjusted Prevalence of Physical Limitations and Poor or Fair Perceived General Health in 2,547[a] Persons With and Without Specific Recent Psychiatric Disorders

Psychiatric Disorder	Any Chronic Activity Restriction		Any Restricted Activity Days in Preceding 2 Weeks		Any Bed Days in Preceding 2 Weeks		Poor or Fair Perceived General Health	
	%	SE	%	SE	%	SE	%	SE
None (N=2,029)	9.0	0.8	9.2	0.7	5.3	0.6	18.5	1.2
Any (N=518)	22.4[b]	2.0	19.2[b]	2.0	12.7[b]	1.7	29.6[b]	2.2
Major affective (N=186)	31.9[b]	3.0	27.4[b]	3.4	16.7[b]	3.3	39.5[b]	4.2
Major depression (N=94)	38.2[b]	3.5	29.1[b]	4.4	23.0[b]	4.2	48.4[b]	4.7
Dysthymic (N=125)	29.4[b]	3.4	27.4[b]	4.2	16.4[b]	4.2	36.5[b]	5.1
Substance use (N=188)	28.1[b]	3.6	14.6	3.8	6.4	2.0	33.7[b]	2.7
Alcohol (N=134)	28.6[b]	4.0	12.3	4.0	7.7	2.9	33.7[b]	3.3
Drugs (N=80)	16.2	5.5	20.9	6.4	7.2	3.0	18.7	5.5
Anxiety (N=205)	24.8[b]	3.7	24.9[b]	3.6	15.9[b]	2.6	30.3[b]	3.5
Schizophrenia/schizophreniform (N=15)	30.0	10.0	24.8	7.5	25.5	7.9	41.2	9.4
Antisocial personality (N=22)	13.1	9.3	17.7	3.6	13.8[b]	2.4	44.5	12.5
Cognitive dysfunction (N=26)	9.5	3.5	2.5	2.5	0.8[b]	0.8	36.1	8.1

[a]Excludes seven persons with missing data on one or more specific psychiatric disorders.
[b]Significantly different ($t>3.30$, $df\geq2,042$, $p<0.001$) from the percentage of persons with no psychiatric disorder who had that type of health problem (top of same column).

and anxiety disorder ($t=4.24$, $df=2,232$, $p<0.001$) than for those with no psychiatric disorder. A similar pattern of results was observed for bed days in the previous 2 weeks. In addition, persons with antisocial personality were significantly more likely to have had a bed day ($t=3.44$, $df=2,049$, $p<0.001$) and those with cognitive dysfunction were significantly less likely to have had a bed day ($t=-4.5$, $df=2,053$, $p<0.001$).

When we examined the effects of any recent psychiatric disorder, any recent chronic medical condition, and their interaction, controlling for sociodemographic factors (i.e., age, sex, ethnicity, job status, education, and marital status) and using multiple regression analysis, both psychiatric disorder and chronic medical condition had significant and independent associations with perceived general health and each physical functioning indicator (for psychiatric disorder, lowest adjusted $\chi^2=9.43$, $df=1$, $p<0.01$, for bed days; for chronic medical condition, lowest $\chi^2=6.42$, $df=1$, $p<0.025$, for bed days). The interactions between psychiatric and medical disorders were not significant in any of the regressions.

When we used separate indicators for any affective, anxiety, substance use, and other psychiatric disorders in regression equations, anxiety disorders were significantly and independently associated with each perceived general health and physical functioning indicator (lowest adjusted $\chi^2=6.83$, $df=1$, $p<0.01$, for chronic limitations); affective disorders were not independently associated with bed days (adjusted $\chi^2=2.42$, $df=1$, $p>0.05$) but were significantly and independently associated with the other functioning indicators (lowest adjusted $\chi^2=7.73$, $df=1$, $p<0.01$, for restricted activity days).

DISCUSSION

We demonstrated that recent psychiatric disorder was strongly associated with perceived general health status and indicators of acute and chronic limitations in physical functioning, even after we controlled for the effects of self-reported chronic medical conditions and demographic factors. For the more chronic physical limitations, the associations with psychiatric disorder were smaller than the associations with chronic medical conditions. For acute physical limitations, the associations with psychiatric disorder were either similar to or larger than the associations with chronic medical conditions.

Several groups of specific psychiatric diagnoses were associated with limitations in physical functioning. The largest effects were for affective disorder, particularly major depression. Other authors have shown that major depression has large effects on social functioning (24–26). Anxiety disorders had consistent and strong associations with limitations in physical functioning. It is not surprising that anxiety disorders affect perceived general health and physical functioning; phobias and panic attacks can lead to restriction of physical activities in order to avoid feared situations. The perception of poor general health could be due to the perception of either the anxiety itself or the accompanying physiological symptoms.

There were only 15 persons with recent schizophrenia or schizophreniform disorder in our sample. While their physical functioning was very poor, our tests were not sufficiently precise to detect this large effect after correcting for multiple comparisons. Future studies should describe the physical functioning of treated

and untreated samples of schizophrenic persons from the community.

The relationships between physical functioning and substance use disorders varied across health indicators. Persons with any substance use disorder were more likely to have a chronic but not acute activity restriction than those with no psychiatric disorder. One explanation for the lack of a significant association between substance use and acute limitations is that substance abuse is a young person's disorder. While our findings were adjusted for sex and age, we may not have been able to completely remove the age effect because of the degree of confounding. Another explanation is that the persons with substance use disorder in our general population sample would be expected to have a relatively mild disorder and thus fewer physical complications.

After adjustment for sociodemographic factors and chronic medical conditions, the psychiatric disorders independently associated with physical functioning were the affective and anxiety disorders. Thus, the effects of substance use disorder on physical functioning appear to be due to associations with depression and anxiety.

To what extent do measures of physical functioning serve as indicators of psychiatric as well as medical disorders? While the magnitude of the association of psychiatric disorder with physical functioning was similar to that with chronic medical conditions, the prevalence of any psychiatric disorder was lower than that of any chronic medical condition. For example, of the respondents included in our analysis, 20.4% (N=521) had a 6-month psychiatric disorder, while 32.9% (N=841) had one or more active chronic medical conditions. The prevalence of major depression, however, was as high as the prevalence of many common chronic medical conditions, such as diabetes (27). Thus, physical functioning reflected the effects of some psychiatric disorders as much as many particular chronic medical conditions.

An important limitation of our data was the reliance on self-reported chronic medical conditions. Persons with psychiatric disorders such as major depression could have falsely attributed somatic manifestations of the psychiatric disorder to a chronic medical condition. We reached the same conclusions about the relationships between psychiatric disorders and physical functioning, however, when we controlled for a more conservative specification of a chronic medical condition, i.e., being under care for the condition. This enhances our confidence in the validity of the main conclusions.

Our results apply to a general population. Previous general population studies have not included measures of both physical functioning and specific psychiatric disorders. The Los Angeles Epidemiologic Catchment Area sample, however, was 50% Mexican-American and thus atypical of the general U.S. population. However, we reached the same conclusions about the relation between physical functioning and psychiatric disorder for both Mexican-Americans and non-Hispanic whites. Our conclusions should be tested in other geographical locations and with other ethnic groups.

In sum, our results suggest that recent psychiatric disorder has a strong association with physical functioning that is independent of the presence or absence of chronic medical conditions. In particular, affective and anxiety disorders emerged as the psychiatric disorders most strongly associated with limitations in physical functioning and perceptions of general health in a general population. The importance of this finding is enhanced by the relatively high prevalence of these disorders in the general population and in the practices of both mental health specialists and nonpsychiatrist physicians.

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Some Differences Between Men and Women Who Commit Suicide

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Men have persistently had a several-fold higher suicide rate than women. In this study of 204 consecutive suicides, the authors examined three areas in which the men differed from the women. Men used more violent, immediately lethal methods of suicide, were almost three times more likely to be substance abusers, and were more likely to have economic problems as stressors. The authors conclude that while the difference in suicide rate between men and women is complexly determined, the weight of the evidence suggests that more men than women intend to commit suicide.

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Since at least 1950, men in the United States have consistently been found to commit suicide 2.5 to 4 times as often as women (1, 2). Data cited by Durkheim from four European countries in the mid-nineteenth century suggest similar ratios (3, p. 101). Several British studies in the modern era, however, have reported ratios closer to 1:1 but still consistently higher rates for men (4–6).

There have been several systematic interview studies about consecutive suicides (6–9), but none of them looked specifically at the issue of why men commit suicide more frequently than women. At least two hypotheses seem worth exploring. The first and more popular is that the same number of women as men intend to commit suicide, but more men are successful because of the choice of methods (10, 11). A second hypothesis is that each sex is equally successful, but more men than women actually intend to commit suicide.

We investigated the cases of 133 individuals under age 30 and 150 individuals age 30 and older who committed suicide in San Diego County between November 1981 and June 1983. In this report, we look specifically at the first 204 consecutive cases and examine some factors that might shed light on the two hypotheses regarding the higher suicide rate by men.

METHOD

The methodology of the study has been described extensively elsewhere (12). During the first 10 months of the study, 204 cases of suicide were collected consecutively. Trained interviewers gathered information from family members, spouses, acquaintances, employers, other witnesses, physicians, and other professionals. The interview form contained over 300 items structured to obtain information about *DSM-III* diagnoses as well as demographic data, stressors at the time of death, and medical and family history. Hospital, physician, therapist, school, and police records were also included when available.

After all data were collected, each case was reviewed independently by two investigators and *DSM-III* diagnoses were made. All diagnoses were systematically considered. Multiple diagnoses were assigned if appropriate. Subjects with more than one diagnosis pertaining to drug and/or alcohol use were counted only once in each designated category.

Information on life events was also reviewed independently by the investigators to determine stressors for each subject. Stressors were defined as events that the investigation indicated were causing the subject distress at the time of death. Anticipated or imagined events, as well as actual events, were included as stressors. The originally described 14 stressor categories (12) were further condensed into seven groups. Death, separation, rejection, and eviction were combined into interpersonal loss/conflict. Financial trouble, job problems, unemployment, and school problems were combined into economic problems. Incarceration and other legal trouble were combined into legal troubles. The other

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TABLE 1. Methods of Suicide Used by 61 Women and 143 Men

Method	Women N	Women %	Men N	Men %
More immediately fatal	26	43	108	75[a]
Firearms	17	28	86	60[b]
Pistol	15	25	56	39
Rifle	2	3	17	12
Shotgun	0	0	13	9
Hanging	4	7	12	8
Jumping	5	8	7	5
Other[c]	0	0	3	2
Less immediately fatal	35	57[a]	35	25
Drug/poison	27	44[d]	16	11
Asphyxia	6	10	14	10
Drowning	1	2	1	1
Cutting	1	2	4	3

[a]$\chi^2=19.1$, df=1, $p<0.001$.
[b]$\chi^2=16.5$, df=1, $p<0.001$.
[c]Includes deliberate automobile wreck, lying on railroad tracks, and jumping in front of a truck.
[d]$\chi^2=26.2$, df=1, $p<0.001$.

groups were illness, family illness, voluntary move, and other. Subjects with more than one stressor in any of the categories (e.g., death of a parent and marital separation) were only counted once for that group (e.g., loss/conflict).

Specific statistical tests for comparisons are indicated in Results and the tables. A probability level of <0.05 was considered significant.

RESULTS

There were 143 men and 61 women in the sample. The vast majority of each group was white (92% of the men and 93% of the women). The mean ±SD ages for the men and women were 43.2±18.7 and 49.1±20.5 years, respectively; this difference was significant (t=2.0, df=202, p=0.046).

The methods that were used to commit suicide are shown in table 1. Men used firearms significantly more frequently and drugs or poison significantly less frequently than women. Similarly, significantly more men used more immediately fatal methods overall.

The frequencies of all diagnoses in the major axes I and II *DSM-III* categories are shown in table 2. Since *DSM-III* allows for multiple diagnoses per person, there are more diagnoses than subjects. Substance use disorders (drug and alcohol) and affective disorders were the most frequent diagnoses for both women and men. There were no significant differences in substance use diagnoses between the sexes. However, there were significantly more major depressive disorders among the women. More men received no diagnosis, but the difference was not significant.

The distribution of stressors is shown in table 3. There were significantly more economic problems among the men than the women.

TABLE 2. Diagnoses of 61 Women and 143 Men Who Committed Suicide

Diagnosis	Women Number of Diagnoses	Women %	Men Number of Diagnoses	Men %
Any diagnosis[a]	94	100	248	100
Drug use disorders	14	15	50	20
Alcohol use disorders	24	26	71	29
Major depression	16	17[b]	17	7
Dysthymic disorder	2	2	3	1
Atypical depression	16	17	40	16
Schizophrenia	0	0	5	2
Atypical psychosis	5	5	11	4
Schizoaffective disorder	0	0	5	2
Schizophreniform disorder	0	0	1	0
Organic mental disorders	3	3	7	3
Adjustment disorders	7	7	21	8
Childhood or adolescent disorders	0	0	3	1
Other axis I disorders	0	0	3	1
Antisocial personality disorders	3	3	7	3
Mixed personality disorder	1	1	0	0
Diagnosis deferred	3	3	4	2
No diagnosis	1		10	
Insufficient information	1		5	

[a]Some subjects received more than one diagnosis.
[b]$\chi^2=6.96$, df=1, p=0.008.

TABLE 3. Stressors of 61 Women and 143 Men Who Committed Suicide

Stressor	Women Number of Stressors	Women %	Men Number of Stressors	Men %
Any stressor	101	100	236	100
Interpersonal loss/conflict	39	39	75	32
Economic problems	15	15	70	30[a]
Illness	25	25	46	19
Legal troubles	4	4	20	8
Voluntary move	5	5	10	4
Family illness	5	5	4	2
Other	8	8	11	5
No stressor	2		5	
Insufficient information	5		0	

[a]$\chi^2=7.5$, df=1, p=0.007.

DISCUSSION

A number of problems face anyone trying to draw conclusions from data collected about suicides. First, most of the information is gathered secondhand and after the fact. As described in more detail elsewhere (12), we have attempted to deal with this by using a structured data base and multiple sources of information.

Second, numbers of cases are always relatively small. While this series represents the largest consecutive series of so extensively studied suicides to date, it still is a limited sample. When limited samples are subdivided by a variety of variables, statistical power

necessarily suffers. Consequently, it is important to try to arrive at acceptable generalities regarding the major variables. In this study those variables were methods of suicide, psychiatric diagnoses, and stressors.

Our division of suicide methods into more and less immediately fatal is somewhat different from the concept of violent suicide (13). Our concept is based on acts that, once started, are not only rapid but difficult to reverse. Slashing may be violent, but the fact is that few people die suddenly from it. We assume that even those who are in the throes of suicidal drive have some notion of how long the method they choose might take.

For our diagnostic framework, we chose *DSM-III*. It has clear advantages over older systems from the standpoint of reliability. It complicates the analysis of individual cases, however, by allowing for multiple diagnoses per subject. This is a problem particularly when multiple substances of abuse are involved. We chose, then, to assign individual subjects to general alcohol and/or drug abuse categories rather than listing every possible substance-use-related diagnosis. This approach loses some diagnostic scope regarding polysubstance abuse, but it simplifies direct comparisons with population data.

Stressors are more of a problem than diagnoses. Nuances are perhaps more important here than anywhere. We know of no good studies that quantitate differences in importance of financial problems, for example, between men and women. Our decisions regarding selection and grouping of stressors were based on generally accepted wisdom but should not preclude more creative divisions in future investigations.

The difference in mean ages between the sexes represents a shift from earlier work (7). The change reflects the subsequent overall increase in younger male suicides, which was the focus of our earlier work (12, 14). The mean ages of the two groups is not a good measure of differences, however, since the male rate is bimodal and the female rate is a rather low flat curve. Different age periods may be important in terms of specific psychiatric diagnoses or stressors, but the mean ages are relatively unimportant.

Our results (table 1) are consistent with U.S. national statistics for 1980, which indicate that more women used drugs or poisons to commit suicide and more men used firearms (2). Even more interesting is the fact that the same number (N=35) of men and women in our sample used less immediately fatal methods. This left the entire difference in rates accounted for by the greater number of men who used more immediately fatal methods. Our data, then, might seem to support the conclusion that the choice of methods protects women (10, 11).

There are several problems with that conclusion. First, a comparison of statistics on suicides between 1970 and 1980 indicates an increase in the use of firearms and explosives by women from 30.2% to 38.6%; in spite of that, the suicide rate for women, if anything, decreased a bit—from 6.8 to 5.4 per 100,000 (2). This apparent decrease, of course, could be insignificant or could be due to other factors such as improved preventive efforts for younger women (15). It does not, however, support the speculation that increasing use of more lethal methods will equalize the suicide rates between men and women (11).

A second problem arises from natural experiments. Several studies have suggested that decreasing the lethality of less immediately fatal methods may positively affect suicide rates (16–18). Such a simple conclusion is highly debatable (19). Nonetheless, there is no way to prove whether such changes affect those who really intend to die or those who may not but underestimate the seriousness of their "attempts."

A third problem is the assumption that people who use less immediately fatal methods but who "truly" intend to commit suicide are, in fact, rescued with some finite frequency. We know of no way to obtain data to prove such a hypothesis. "True" intent to commit suicide is something that, unfortunately, can only be inferred after the fact. Because women may attempt suicide twice as often as men (20), one cannot conclude that they intend for the attempts to be fatal twice as often as men do.

It is possible, then, that women and men who are "truly" suicidal could be equally successful in their attempts. If that were the case, the difference in rates would have to be explained by the fact that more men than women actually intend to commit suicide.

The vast majority of persons who commit suicide suffer from psychiatric disorders and psychosocial stressors (12). It seems reasonable, then, to look at these factors for possible explanations as to why more men than women might intend to commit suicide.

The most common psychiatric diagnoses for both women and men in our sample, as well as in the other systematic interview studies, were substance abuse and affective disorder (6–9). We compared the number of subjects in our sample with alcoholism, drug abuse, and major depressive diagnoses to the 6-month prevalence rates reported by the recent epidemiological study sponsored by the National Institute of Mental Health (NIMH) (21) (table 4). For this comparison, we combined major depression and atypical depression (no subject received both diagnoses). Subjects with atypical depression met the criteria for major depression but were given the diagnosis of atypical depression because of confusion over the relationship to substance abuse (12). They would most likely have been included in the major depressive group in the NIMH study. Like ours, the NIMH diagnoses were not mutually exclusive.

Three observations emerge from this comparison. First, alcoholism, drug abuse, and depression were much more common among both the men and women who committed suicide than in the general population. Second, within the group who committed suicide, there were no significant differences between men and women in the presence of alcoholism, drug abuse, or depression. Third, in the general population depres-

TABLE 4. Diagnoses in an NIMH General Population Study and in Subjects Over Age 17 in the Present Study of Suicide

Diagnosis	NIMH Study (21) (%) (mean of three sites)		Present Study			
			Women (N=60)		Men (N=141)	
	Women (N=5,727)	Men (N=3,816)	N	%	N	%
Alcoholism[a]	4.4	24.3	20	33	60	43
Drug abuse	4.4	7.0	13	22	50	35
Major depression[b]	7.2	3.1	32	53	56	40

[a]Does not include cases where alcohol intoxication was the only alcohol-related diagnosis.
[b]In the present study, includes major depression and atypical depression.

sion is about twice as common in women and drug abuse twice as common in men, factors that might cancel each other out if each were equally lethal vis-à-vis suicide. Alcoholism, on the other hand, was five times more frequent in men than women in the NIMH population study. The mortality rates from suicide among depressed and alcoholic subjects are reported to be rather stable (22, 23). Given that the rates of suicide or depression and alcoholism are relatively stable (24), it follows that the greater suicide rate in men could partly or mostly be due to their greater rate of alcoholism.

Suicide rates deal with individual cases rather than diagnoses, however. Previous reports have indicated that alcoholics with and without depression were very similar (25) and that alcoholics with depression were more like pure alcoholics than pure depressive subjects (26). For our second diagnostic comparison, then, we placed subjects with both substance abuse (alcohol and/or drugs) and a depressive disorder or any other diagnosis in the substance abuse group. When we did that, we found that the actual number of suicides by the substance abusers was 2.7 times greater for men than women (74 versus 27), well within the range of the male/female suicide ratio. This gives more support to the possibility that more men than women intend to commit suicide because of the greater frequency of substance abuse.

The greater rate of substance abuse seems to provide only a partial explanation, however. The number of suicides by pure depressive subjects (i.e., with diagnoses of major depression, dysthymic disorder, and atypical depression) was about equal for men and women (21 versus 18). The ratio of men to women in the remaining cases (48 versus 16), however, was even greater than that for the substance abusers. They were for the most part divided among 12 other diagnoses. The number of men and women in the other major categories were as follows: psychotic disorders, N=9 and N=2, respectively; adjustment disorders, N=17 and N=5; miscellaneous disorders, N=5 and N=4; deferred/insufficient data, N=7 and N=4; and no disorder, N=10 and N=1. The numbers in the other diagnostic categories were too small for both our sample and the NIMH population study (21) to lead to specific conclusions for each of them. It is possible, however, that all the disorders (except for affective disorders) which occur among subjects who commit suicide are more frequent among men. It does appear that the higher suicide rate in men is not limited to a single psychiatric diagnostic category such as substance abuse.

Another reason that more men than women may intend to commit suicide may be that men are subject to more psychosocial stressors than women. Like psychiatric disorders, the vast majority of our subjects of both sexes were judged to have meaningful stressors at the time of death (table 3). The only significant difference between the sexes in our sample was for economic problems. The complexities of relating life events to illness have been thoroughly reviewed (27) and can be expected to apply to the suicide problem. Also, the rates of various stressors in the general population are not known. Without that information, further speculation regarding their significance to suicide is just that. The possibility that greater economic or other stressors contribute to the higher suicide rate in men cannot be eliminated on this basis, however. If true, it would lend greater weight to the argument that more men than women may intend to commit suicide.

None of the three factors discussed here is clearly identified as the major contributor to the difference in suicide rates between the sexes. We believe our data favor the conclusion that the major reason more men than women in the United States commit suicide is that more men intend to do it. Of the two factors related to intent that are investigated here (i.e., method of suicide and psychiatric diagnosis), psychiatric diagnosis has perhaps the greater potential clinical importance. If, as we suspect, the biggest reason for the differential suicide rate between women and men is the greater amount of substance abuse among men, the implications are clear. From a public health standpoint, substance abuse education, identification, and treatment are crucial. This would obviously not be an answer to the whole suicide problem; hopefully, however, it would lead to narrowing the suicide gap between men and women on the low side.

It makes sense to do what can be done, both publicly and in individual cases, in terms of modifying the lethality or availability of suicide methods. It is not clear whether such practices are indeed effective. As clinicians know, it is difficult to separate suicidal persons from all available methods, even in the hospital (28).

Firm conclusions regarding the clinical usefulness of stressors in predicting or preventing suicide will require greater development of the epidemiology of stressors.

Finally, it would be injudicious to assume that the variables addressed here were either the right ones or the only ones of importance to this issue. The three we

chose to examine here have been repeatedly found to be important in studies of suicide and were addressable with our data base. Many other factors, including genetics (29) and personality characteristics (30), have been suggested as major contributing causes of suicide. Future investigations should continue to seek other factors of importance and to examine different relationships between known factors and systematically gathered data.

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How to Survive in the Private Practice of Psychiatry

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The private practice of psychiatry is being transformed by the new economics of medical care. Patients are paying more out-of-pocket for necessary care (demand-side cost sharing), and health care providers are being asked to assume part of the risk of treatment through prospective payment (supply-side cost sharing). Specific survival strategies for psychiatrists in private practice include development of a balanced practice, expansion of referral networks, participation in alternative delivery systems such as health maintenance organizations and preferred provider organizations, active involvement in utilization and claims review, participation in outcome studies, and expansion of patient care advocacy and community involvement.
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Dramatic changes in the economics and delivery of medical care in the United States have been alternatively called "industrialization," "corporatization," and "social transformation" (1). The dawn of the era of medical big business has arrived. Can the individual physician in private practice survive? What will happen to the office-practice psychiatrist? Are there elements of private practice that can be preserved, even as large medical conglomerates form and physicians are faced with the choice of either becoming part of so-called "supermeds" or being left out of the market for health care services altogether? What are the issues for our patients especially, as they face the bewildering array of choices of alternative delivery systems such as health maintenance organizations (HMOs), preferred provider organizations, for-profit medical delivery systems, and large medical care industries?

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THE TRANSFORMATION OF PRIVATE PRACTICE

Where there is a two-party transaction for medical care between a physician and a patient, the economic rules are straightforward. The physician establishes the parameters of his or her practice, including a fee; the patient hires a physician at an agreed-upon fee and has the option of firing the physician. If there are sufficient numbers of physicians or other providers of medical care, the rules of price competition make this system cost-efficient.

This is not the case today in American medicine and probably never was. Rather, the demand for medical care has been and is, for the most part, determined by physicians' decisions, such as whether to order laboratory tests and whether to hospitalize. The definitions of health and illness reside largely with the physician, and until recently there has been a shortage of physicians in most areas of the country and in most specialties of medicine.

In the two-party transaction, the physician determines his or her own economics, including personal economic goals, hours of work, and, in part, the quality of care delivered. Concern for the patient is tempered by the capacity of the patient to pay. However, when the costs of expensive care, especially hospital care, began to be beyond the reach of the majority of Americans, the so-called "third party" was invented. Threesomes are infinitely more complicated than twosomes, as we know from psychiatry.

At first, hospitals and physicians welcomed third-party payments as a way of removing the economic barrier to more extensive care. As long as the essential features of the two-party relationship remained—with patients continuing to choose their physicians, physi-

cians setting their fees, and third parties paying those fees—all was well. However, this retrospective, cost-based reimbursement system and other factors have led to cost containment problems in health care delivery. Cost sharing by patients is increasing, and economic risk taking by health care providers is proposed as the solution to these escalating costs.

On the demand side, third-party payers have begun to insist that patients assume more of the fiscal decision making and cost sharing in choosing the method and type of insurance coverage, the levels of deductibles and copayments, and the out-of-pocket payments, especially upon receipt of service. This reduces the cost of medical care by reducing demand and utilization (2). However, this is not a very popular alternative, since most individuals prefer to receive medical care without facing bankruptcy at the same time.

A much more politically acceptable option is supply-side cost sharing, in which third parties impose risk-sharing arrangements on health care providers in an effort to lower utilization. The elements of these transactions are essentially similar, whether the risk sharing involves the new regulatory standards embodied in diagnosis-related groups (Medicare's prospective payment system, based on 468 different products or groupings of care delivery), a capitation approach such as HMOs use, or a mixed system such as that used by independent practice associations and preferred provider organizations. Money is provided for the delivery of care before the care is provided, and through this prospective payment, providers are challenged to come up with effective and efficient ways of delivering care. It is supply-side cost sharing that undergirds the social transformation of American medicine and that has led to the emergence of a new corporation-owned cottage industry of medical practice.

However, these efforts at cost containment appear also to compromise access to care, quality of care, and some of the basic freedoms of practice. It is in this last category, basic freedoms of practice, that some of the essential elements of private practice may be sacrificed, such as the patient's free choice of physician, the physician's free setting of fees, and the freedom to determine the kind and level of services. The current surplus of physicians and hospital beds, leading to a "buyer's market" for medical care, permits supply-side cost sharing to escalate. What is remarkable now is the overwhelming consensus on the part of big business, labor, insurance companies, and government that they all must become "prudent buyers" of medical care and not allow their own previously acceptable passive role to continue.

How can physicians respond to the new regulations, which are establishing more market-based incentives for the delivery of health care? Is it possible to fashion this system, control it, and preserve the essential elements of private practice? Can the private practice of psychiatry survive in the face of this overarching challenge? Before discussing strategies for adaptation and survival, we present a recent case history and a review of the current status of private practice.

What Happens in California Can Spread Like a Canyon Fire

A recent California Medical Association survey (3) showed that almost all California physicians have been approached by prospective payment organizations and HMOs with offers to provide services under contract. Ninety-six percent of the 675 survey respondents reported having been offered at least one contract with a preferred provider organization, and 79% had had at least one offer from an HMO. Most had received multiple offers. Seventy-five percent of the physicians had signed at least one contract with a preferred provider organization; 54% had signed at least one HMO contract. Physicians in all categories—young, old, urban, rural, solo practice, group practice, general practice, and specialty practice—had signed such contracts. These arrangements have resulted in their seeing more patients and receiving less than the usual and customary fees, with a possible decrease in practice revenues.

The most prevalent pattern among these physicians was entering into two to four separate contracts. These contracts emphasize fixed fee schedules or schedules of maximum allowances, participation in risk pools, reimbursement for only a percentage of the physicians' individual charges, payment based on a proportion of the community's prevailing fees, and capitation arrangements. Only 7% of the respondents reported having received an increase in their practice revenues as a result of participating in these contract plans.

It is not only in California that such activity is taking place. Recently, the Empire Blue Cross and Blue Shield Program of New York contracted with 5,800 of 7,300 physicians in New York to join a new independent practice association type of HMO (4).

Although many individuals may have chosen medicine in order to avoid complex business choices, this new competitive era challenges every physician to make certain economic decisions that may be difficult, even distasteful, and that raise questions about the quality of medical care.

The Private Practice of Psychiatry

Office-based practice is the primary work setting for 66% of all physicians (5) and 58% of all psychiatrists (6). Most psychiatrists work in more than one setting during the course of a week (7). Of all active practicing psychiatrists, 70% work in two or more settings and 30% in three or more settings per week. Private practice is the most common secondary work setting for individuals who have another primary work setting, such as a hospital practice. Thirty-four percent of psychiatrists whose primary employment setting is private practice report secondary employment in pri-

vate practice as well. For all psychiatrists, almost 90% of their time is spent in direct patient care.

Outpatient psychiatric services are poorly covered by insurance. Almost one-fourth of psychiatrists' private-practice outpatients pay their costs totally out-of-pocket. More than half pay at least 50% of the costs out-of-pocket. This proportion varies according to insurance markets across the country and differs in different states. According to the Continuing Survey of Medical Economics, out-of-pocket payments by patients account for 25% of the typical physician's gross income and 40% of the typical psychiatrist's gross income (8). This difference reflects the fact that private health insurance for the treatment of mental disorders is more restrictive (high deductibles and copayments, dollar and visit limits) than coverage for other illnesses (9). Despite these restrictions, office-based psychiatrists in private practice have the highest earnings among psychiatrists, and psychiatrists are the highest-paid "cognitive" medical specialists (10). The competition for patients includes primary care practitioners, who increasingly serve as gatekeepers for all specialty care. They have a strong interest in the direct treatment of mental disorders. Also, there has been a dramatic increase in nonphysician mental health professionals, such as psychologists and social workers, who have become private-practice psychotherapists in many communities across the country. These competitive pressures keep fees low and create cost problems for third parties because of the potentially large volume of patients seen by an ever-increasing supply of providers (11).

STRATEGIES FOR ADAPTATION AND SURVIVAL

Private practice in our pluralistic and mixed system will continue primarily because patients and physicians prefer the privacy of this arrangement, in which the physician contracts with the patient and confidentiality is ensured. This arrangement ensures the ability of physicians to spend the needed time with patients, allows a focus on quality, and supports the delivery of personal care. Since these elements are valued and individuals prefer them, the model will continue to survive even with the pressures for cost-efficiency.

This is not to say, however, that every practitioner will survive in private practice, and those who continue to practice without developing certain kinds of strategies will find themselves out in the cold. The following strategies are suggested for increasing the potential for a successful private-practice adaptation in the face of these revolutionary economic and delivery system trends.

Development of a Balanced Practice

Psychiatrists who desire to maintain a full-time practice with a primary orientation toward intensive and long-term psychotherapy and psychoanalysis may soon find that it is not possible to focus exclusively on patients in need of those services and still remain in practice. Referrals for intensive psychotherapy and psychoanalysis could become scarcer, and third parties are already more reluctant to provide necessary insurance coverage: limits on numbers of visits and lifetime dollar limits have increased (12). Other types of patients whose needs are congenial with the techniques and environment of long-term, intensive psychotherapy should be sought. These include patients with substance abuse problems who have complex underlying personality disorders but who are not amenable to long-term intensive psychotherapy. They should have a comprehensive evaluation performed by a psychiatrist trained in psychodynamic principles. Similarly, nonpsychotic patients with severe psychosomatic problems and borderline conditions are suitable for inclusion in the practice of psychodynamically oriented psychiatrists.

The broadening of the office case mix should be consistent with the self-perception and skills of the individual private psychiatrist; broadening the mix is important for the future viability of a private practice. Psychodynamically oriented psychiatrists should be familiar with basic psychopharmacologic principles and be competent to prescribe psychoactive medications. They should be skilled in short-term psychotherapy, evaluation, and referrals as well.

Expansion of the Referral Network

Office-based private psychiatrists tend to isolate themselves not only from their own professional peers but also from other medical colleagues and mental health professionals. Cultivating relations with these colleagues as possible sources of referrals is the sine qua non of successful marketing. The special skills and capacities of the private psychiatrist should be communicated to these referral networks through a process of patient feedback and follow-up. There are some patients for whom the private-office psychiatrist should provide primarily consulting services to the referring physician or mental health professional. There are others, depending on the basis of the referral, who require ongoing treatment by the psychiatrist. In either case, a letter communicating the findings and a treatment plan is an excellent technique for maintaining one's referral network. The capacity to communicate fully to referring physicians and other professionals should be part of every psychiatrist's training and background.

By participating more actively in hospital medical staff committees and activities, psychiatrists can better learn what their medical colleagues desire in response to their consultation requests. Written consultation reports containing clear clinical descriptions and explanations accompanied by concise recommendations, similar to consultation/liaison reports in general hospitals, will add to the credibility, standing, and referral base of private-practice psychiatrists.

The smaller the private practice and the fewer the patients a private psychiatrist has in treatment at any given time, the larger the referral basis must be for survival in hard economic times. If the psychiatrist desires to treat a few appropriate patients intensively and extensively, he or she must evaluate many more people to find the right patients. Many patients who can benefit from diagnosis and treatment by a private psychiatrist do not come to the psychiatrist first; they more often seek help from a general practitioner, an internist, another mental health professional, a provider of social services, or a member of the clergy. Unless the private-practice psychiatrist establishes strong relationships with other sectors of the caregiving professions, referrals are likely to go elsewhere. Even so, it may be necessary to expand one's "market" by joining a preferred provider organization or contracting with an HMO. In very competitive situations, psychiatrists may have to consider a judicious advertising campaign, specially focused on the trade magazines read by general physicians and mental health professionals. Private hospitals have led the way in media-based advertising, which has expanded the referral base for inpatient care and led to a general lowering of the stigma involved in seeking psychiatric treatment. Consultation with a marketing and advertising expert is very helpful in preparing such strategies.

Participation in Selected Organizations

Psychiatrists in private practice should not isolate themselves from new alternative delivery systems, since the new competitive environment in this era of managed health care requires increased opportunities to negotiate successfully for access to patients. Preferred provider organizations, independent practice associations, and HMOs are arrangements that have the potential for allowing private-practice psychiatrists to remain independent while they enter into specific contractual negotiations which enable them to determine the conditions of practice as well as price.

In this context, many physicians may be forced to deal with the issue of discounting services as a way to ensure fully subscribed practices serving different types of patients. Psychiatrists must learn the economic basis for discounting services if they are to cope with it. These contractual arrangements must be distinguished from those in fully salaried corporate employment situations or in HMOs that have closed staffs. A further step would be for psychiatrists in private practice to band together with their medical colleagues as well as other nonmedical mental health professionals to form preferred provider organizations or independent practice associations so as to control and direct their own futures (13). However, before forming or joining one of these organizations, psychiatrists should seek legal counsel, and agreements should be carefully reviewed by legal counsel to avoid antitrust and other potential legal complications.

Active Involvement in Utilization and Claims Review

It is essential for private-practice psychiatrists to understand that in this new era of managed care, the processes of utilization and claims review are inevitable and must be embraced as an alternative to arbitrary caps on benefits. Indeed, private psychiatrists should devote part of their time to such activities, since they will determine the scope of practice. Reimbursement for long-term psychotherapy will require such review, and the development of proper claims and utilization review procedures leading to formal peer review will ensure that these procedures appropriately identify the kinds of patients who require long-term psychotherapy and who should be approved for continuing care.

Participation in claims and utilization review will help psychiatrists in private practice to define the nature of severe mental illness so that "catastrophic" illness benefits can be provided to those patients who will benefit most from intensive and long-term psychotherapy and extensive inpatient stays. Such participation will also lead to greater understanding of and support for other treatment strategies, such as time-limited psychotherapy, shorter inpatient stays combined with more lengthy day treatment, and the expanded use of psychosocial rehabilitation services for persons with chronic mental illness.

Participation in Outcome Studies

The current era has been described as experiencing a crisis in cost-effectiveness. Unless certain medical treatments can demonstrate their efficacy as well as their cost-efficiency, it will be difficult to continue to find the necessary reimbursement for them. Long-term psychotherapy has been criticized for its inability to demonstrate clearly that its cost-effectiveness goes beyond that of the shorter-term psychotherapies. With the increasing research attention to biological psychiatry, the emphasis on determining the scientific basis for psychotherapy has increased even more. Therefore, practitioners of office psychotherapy must be willing to engage in the research needed to underscore the validity of this therapy.

The medical outcome study recently launched by the Rand Corporation is an example of such research. The Rand medical outcome study will measure the outcomes of care for adults with chronic disease and the health costs in a variety of health care settings, including private practice. The settings to be evaluated include HMOs, large, multispecialty, fee-for-service group practices, and small group and solo fee-for-service practitioners. The specific chronic diseases to be studied include advanced coronary artery disease, diabetes, high blood pressure, and depression. The outcomes of care of depressed patients by psychiatrists in a variety of settings will be compared with one another as well as with general physicians' management of depressive illness (14). Only with an adequate base of such knowledge can medical practitioners

demonstrate that what they do is efficacious and worthy of reimbursement.

Patient Care Advocacy and Community Involvement

The isolation of office-practice psychiatrists from their medical colleagues and mental health professionals is mirrored by their isolation from community advocates who might be extremely effective in arguing for higher levels of reimbursement. A number of support groups, including those which focus on family members of the mentally ill, have expanded dramatically and are focusing on reimbursement questions. Relations with these groups need to be cultivated by psychiatrists, including those who concentrate on long-term psychotherapy. When state legislatures and others hold hearings on the necessity of adequate third-party reimbursement, patients and their families have greater credibility than health care providers. The strategy of mandating mental illness benefits through state insurance laws can be successful only with the help of a coalition of advocacy groups that include not only the mental health professions and psychiatry but also patient support groups.

CONCLUSIONS

We have made these suggestions in an effort to alert private-office psychiatrists to a number of proactive steps that they might take in order to handle an uncertain future. Expanding the scope of one's practice, building referral networks, increasing community involvement, enhancing the data base on which one's practice rests, becoming involved in utilization and claims review, and participating in selected alternative delivery systems are all approaches designed to handle whatever future conditions may impinge on the private practice of psychiatry.

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Effects of Diagnosis and Context on Dangerousness

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The authors extensively reviewed the medical records of 253 patients hospitalized on a locked, university-based psychiatric unit. They found that schizophrenic and manic patients were more likely than patients with other diagnoses to be assaultive before admission. In the hospital, however, manic patients were the most likely to be assaultive. The results of this study show that the risk of violence among different diagnostic groups of patients varies according to context and is moderated by situational variables. These findings have implications for the assessment of dangerousness before and during hospitalization.

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Although the overall prevalence of violence among the mentally ill is a subject of controversy (1), there is a growing consensus that acute mental illness of sufficient severity to warrant hospitalization is frequently accompanied by violent behavior (2–5). Some findings suggest that clinical variables such as diagnosis are more important risk factors for violence in the period surrounding hospitalization than are demographic characteristics (3, 5, 6). However, studies of the nature of the relationship between specific diagnoses and assaultive behavior have had contradictory results.

For example, several studies have found that schizophrenic patients are more likely than other patients to be violent in the period preceding hospitalization (3, 7–9) and to be assaultive in the hospital (9–11). Tardiff (4), however, presented data indicating that during hospitalization, schizophrenic patients are *less* likely to be violent than other patients. Tardiff (4) has suggested that the relative risk of violence by schizophrenic patients varies depending on whether the patients are in the hospital or not. To our knowledge, no studies have followed the same group of schizophrenic patients in both the preadmission and acute hospitalization periods.

Acutely manic patients represent another diagnostic group with a high potential for loss of impulse control, which could result in violence. Few studies, however, have investigated the extent of violence among acutely manic patients. Studies of violent behavior have often compared patients with schizophrenic diagnoses to patients with nonschizophrenic diagnoses, without specifically examining manic patients (8, 11–13). Some studies have grouped paranoid schizophrenia and mania together, as distinguished from nonparanoid schizophrenia (7, 14). Two studies which did examine the preadmission behavior of manic patients reported that mania was associated with high levels of agitation, anger, and fear-inducing behavior but not actual assaultiveness (3, 5). On the basis of his research on the preadmission behavior of patients who were subsequently hospitalized, Craig (3) hypothesized that "manic patients . . . seem to have sufficient impulse control to avoid overt assaultive behavior. For them, adequate medical intervention in a relatively less restrictive environment (e.g., a day hospital) may be optimal." In contrast, Yesavage (15) has shown that manic patients may be liable to commit assaults in the hospital. There has been little direct study of the relative risk of violence in the hospital by manic patients, as compared to schizophrenic patients and patients with other diagnoses.

Previous authors (4, 16, 17) have suggested, on the basis of extensive review of empirical research on

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violence, that a full understanding of violent behavior must take into account both situational factors and the characteristics of the potentially violent person. To our knowledge, the possible role of situational variables in moderating the relationship between diagnosis and the potential for violence has not been directly studied with acute psychiatric patients. This report investigates the interaction between the nature of patients' underlying psychopathology (i.e., diagnosis), context (i.e., community versus hospital), and violent behavior.

This study addressed the following questions: 1) Are schizophrenic patients, manic patients, or patients with other diagnoses most likely to be assaultive before admission and 2) are schizophrenic patients, manic patients, or patients with other diagnoses most likely to be assaultive during the acute phase of hospitalization?

METHOD

The setting was a locked, short-term, inpatient psychiatric unit in a university hospital. The unit provides psychiatric services for an urban, middle-class catchment area of approximately 200,000. Subjects were drawn from 150 patients randomly selected from all the patients admitted during 1983 (N=238) and during the first 6 months of 1984 (N=118). After removal of multiple admissions, 253 patients were retained for study.

The medical record of each patient was reviewed for diagnosis and demographic information including sex, age, ethnicity, and social class. Diagnosis was based on *ICD-9*, Clinical Modification. Social class was computed on the basis of a combination of occupational and educational information according to Hollingshead's formula for the Two-Factor Index of Social Position (18). In addition, charts were extensively reviewed for evidence of violence in two different settings: before admission and during acute hospitalization.

Preadmission violence was defined as encompassing the period of 2 weeks before hospitalization. This time period was chosen because a previous study of ours (19) showed that there is a high rate of violent behavior during the 2 weeks before admission. Hospital violence was measured during the first 24 hours of hospitalization, since previous research by our group (2) has shown that the highest rate of violence is in this time period (2). Violent behavior was rated according to an adaptation of the scale developed by Lagos et al. (20). The revised scale consists of four categories of violent behavior—attacks on persons, attacks on objects, threats to attack persons, and verbal attacks on persons. If a given record indicated that more than one of the four types of violence had occurred, only the most serious description was tabulated. Charts were reviewed by six experienced clinical staff members who completed training in the rating system to a criterion interrater agreement (21) of kappa=0.80 before they began the chart reviews. For purposes of data analysis, the Lagos et al. rating scale was combined into three levels of increasingly severe violent behavior: no violence, fear-inducing behavior (verbal attacks, threats to attack, or attacks on objects), and attacks on persons.

RESULTS

For purposes of data analysis, patients were divided into three diagnostic groups: schizophrenia, mania (including manic disorder, bipolar affective disorder, manic or mixed, and atypical manic disorder), and all other diagnostic categories. Of the 253 patients, 34.4% (N=87) were schizophrenic, 18.2% (N=46) were manic, and 47.4% (N=120) had other diagnoses (i.e., major depressive disorders [N=19], other affective psychoses [N=11], paranoid states [N=8], other nonorganic psychoses [N=20], organic psychotic conditions [N=14], personality disorders [N=22], adjustment reactions [N=10], and other diagnoses [N=16]). Demographic information about the patients in each diagnostic group is summarized in table 1. As can be seen, there was no statistically significant difference in ethnicity or social class among the diagnostic groups. Most of the patients in all three diagnostic groups were Caucasian and in the lowest social class. However, the three groups differed significantly in sex and age. The schizophrenic patients were more likely to be male and younger than patients in the other diagnostic groups.

When we looked at violence in the community, we found that 21.0% (N=53) of the patients had attacked persons and 25.3% (N=64) had engaged in fear-inducing behavior during the 2 weeks before admission. Table 2 shows the type of preadmission violence for patients in the three diagnostic categories. Chi-square analysis revealed a significant association between diagnosis and the occurrence of violence. As can be seen, schizophrenic and manic patients were almost equally likely to attack persons before admission and were much more likely to attack persons than were patients with other diagnoses. Schizophrenic patients were more likely than manic patients to engage in fear-inducing behavior, and both schizophrenic and manic patients were more likely to engage in fear-inducing behavior than patients with other diagnoses.

Since the distribution of patients according to sex and age differed between diagnostic categories, we repeated the preceding analyses separately for men and women and for younger (18–39 years) and older (40 years or older) patients. The same patterns of associations between diagnosis and violence described in the preceding paragraph were replicated for men (χ^2= 14.39, df=4, $p<0.01$) and for younger patients (χ^2=19.85, df=4, $p<0.001$). Although not statistically significant, a similar pattern was present among the female patients and the older patients.

Examination of the patients' behaviors during the first 24 hours of hospitalization showed that 13.0% (N=33) attacked persons and 32.0% (N=81) engaged

TABLE 1. Demographic Characteristics of Schizophrenic, Manic, and Other Patients on a Locked Psychiatric Unit

Characteristic	Schizophrenic Patients (N=87)		Manic Patients (N=46)		Other Patients (N=120)		Total[a] (N=253)		Significance		
	N	%	N	%	N	%	N	%	χ^2	df	p
Sex									10.71	2	<0.01
Female	30	34.5	22	47.8	69	57.5	121	47.8			
Male	57	65.5	24	52.2	51	42.5	132	52.2			
Age (years)									15.30	6	<0.02
18–29	32	36.8	11	23.9	40	33.3	83	32.8			
30–39	33	37.9	17	37.0	33	27.5	83	32.8			
40–49	12	13.8	11	23.9	13	10.8	36	14.2			
≥50	10	11.5	7	15.2	34	28.3	51	20.2			
Ethnicity									10.55	6	n.s.
Black	13	14.9	4	8.7	16	13.3	33	13.0			
Caucasian	43	49.4	31	67.4	75	62.5	149	58.9			
Asian	23	26.4	5	10.9	15	12.5	43	17.0			
Other	8	9.2	6	13.0	14	11.7	28	11.1			
Social class									22.24	6	n.s.
I	0	0.0	1	2.2	0	0.0	1	0.4			
II	0	0.0	3	6.5	1	0.8	4	1.6			
III	0	0.0	2	4.4	9	7.5	11	4.4			
IV	17	19.5	10	21.7	30	25.0	57	22.5			
V	70	80.5	30	65.2	80	66.7	180	71.2			

[a]Not included in the chi-square analyses.

TABLE 2. Violence in the Community and During Short-Term Hospitalization by Schizophrenic, Manic, and Other Psychiatric Patients

Violence and Setting	Schizophrenic Patients (N=87)		Manic Patients (N=46)		Other Patients (N=120)		Total[a] (N=253)		Significance		
	N	%	N	%	N	%	N	%	χ^2	df	p
Community									26.09	4	<0.0001
Attacks on persons	23	26.4	14	30.4	16	13.3	53	20.9			
Fear-inducing behavior	32	36.8	12	26.1	20	16.7	64	25.3			
No violence	32	36.8	20	43.5	84	70.0	136	53.8			
Hospital									15.53	4	<0.004
Attacks on persons	9	10.3	12	26.1	12	10.0	33	13.0			
Fear-inducing behavior	37	42.5	13	28.3	31	25.8	81	32.0			
No violence	41	47.1	21	45.7	77	64.2	139	54.9			

[a]Not included in the chi-square analyses.

in fear-inducing behavior. Table 2 shows the type of violence in the hospital for patients in the three diagnostic categories. Chi-square analysis revealed a significant association between diagnosis and violence; however, the nature of the relationship between diagnosis and violence was different from that in the preadmission period. Manic patients were most likely to attack persons during the first 24 hours of hospitalization. Schizophrenic patients were the most likely to engage in fear-inducing behavior.

The same pattern of association between diagnosis and inpatient violence was observed with the subgroup of male patients ($\chi^2=10.69$, df=4, $p<0.03$), younger patients (18–39 years) ($\chi^2=12.33$, df=4, $p<0.02$), and older patients (40 years or older) ($\chi^2=12.83$, df=4, $p<0.02$). A similar pattern was present among the female patients, but the degree of association did not reach statistical significance. These findings suggest that sex and age cannot explain the observed association between diagnosis and violence during acute hospitalization.

DISCUSSION

To our knowledge, this is the first study of the relationship between diagnosis and violence that has followed the same group of acutely ill patients in different settings (i.e., before admission and during hospitalization). Our findings suggest that the risk of violence by different diagnostic groups varies according to context. In the community during the period before hospitalization, both schizophrenic and manic patients had a higher risk of assaultive behavior than patients with other diagnoses. During acute hospitalization, however, manic patients were more likely to be assaultive than schizophrenic patients and patients with other diagnoses. These results support the

hypothesis of previous authors (4, 16, 17) about the important role of situational variables in violent behavior.

Both the diagnoses of schizophrenia and mania were associated with dangerous behavior before admission. Since both of the major functional psychoses are correlated with dangerousness before admission, it may be that in the unstructured community setting, the important variable is acute psychosis, rather than specific diagnosis. That is, a decompensating patient with poor impulse control may be at risk for violence in the community regardless of the diagnosis. Although other investigators have also found that schizophrenic patients are overrepresented in the group of patients who are violent in the community (3, 5, 7, 8), our finding that acute mania is also associated with violence in the community has, to our knowledge, not been previously reported. In fact, our findings about mania differ from those of previous studies which suggested that manic patients are unlikely to be assaultive in the community (3, 5). In view of this inconsistency, the issue of dangerousness of acute manic patients in the community remains an open question.

During the acute phase of hospitalization, we found that manic patients were most likely to be assaultive and that schizophrenic patients were relatively less likely to be assaultive. The finding about the schizophrenic patients is similar to that of Tardiff and contrary to the findings of other investigators (6, 9–11).

Our finding that the frequency of violence by schizophrenic patients decreases after admission is evidence that situational and treatment variables modify the likelihood of violence. During the first 24 hours of hospitalization, schizophrenic patients are given neuroleptics, which decrease psychotic symptoms and cause sedation. Obviously, this may decrease the likelihood of violence. In addition, the structure of the hospital setting, as well as verbal interventions by staff and the use of seclusion, may play a role in decreasing the frequency of violence.

To our knowledge, our finding that manic patients are the most likely diagnostic group to be assaultive during the initial phase of hospitalization has not been previously reported. Our data do not provide definitive explanations for this phenomenon. It is possible that the irritability and lability characteristic of manic patients may make them more prone to unpredictable assaultive behavior compared to schizophrenic patients. At one moment manic patients may seem relatively in control of their behavior, and at another moment, especially if they feel that their needs are not being met, they can be explosive and out of control (22). It is possible that staff may not be as aware of the assaultive potential of manic patients because of their periods of relative control. Therefore, staff may be less likely to quickly and preventively intervene with medications, seclusion, and verbal interventions; and a manic patient's behavior may rapidly escalate, and he or she may become assaultive.

A possible confounding variable in our results is the fact that the three diagnostic groups had different demographic characteristics. The schizophrenic patients were more likely to be male and younger than the patients in the other two diagnostic groups. Since previous studies have shown that younger age and being male are risk factors for violence (16), it could be postulated that the age and sex of our patients were the more important variables related to violence, rather than diagnosis. However, when demographic variables were controlled (i.e., by stratifying patients by age and sex), the associations we observed between violence and diagnosis generally remained.

Our findings have several implications. First, our study has implications for hospital management of manic patients. Our data show that during the first 24 hours of hospitalization, staff need to pay particular attention to the violence potential of manic patients and, thus, prevent assaultive behavior and injury. Moreover, our study has implications for assessing dangerousness and making decisions about civil commitment. Our data show that clinical variables such as diagnosis should be examined in light of the moderating influence of situational variables. For example, acutely psychotic patients in general may be more likely than other patients to be assaultive before hospitalization. Yet, during acute hospitalization, the specific diagnosis of mania or schizophrenia is a more important variable in predicting dangerousness.

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Epinephrine Infusions in Patients With Social Phobia

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To assess the role of peripheral epinephrine in social anxiety, the authors infused 11 patients meeting DSM-III *criteria for social phobia with intravenous epinephrine over 60 minutes. Although the mean plasma epinephrine level increased from 113 to 928 pg/ml, only one of the 11 patients experienced observable anxiety; this finding suggests that an increase in plasma epinephrine level alone is inadequate to cause social anxiety. Of the variables measured, only the average minute volume correlated with self-rated anxiety. Ventilatory indexes might be better correlates of subjective anxiety than other physiological variables.*
(Am J Psychiatry 1988; 145:733–736)

Patients with social phobia are prone to symptoms indicative of peripheral autonomic arousal. The belief that others will notice these symptoms exacerbates their fear of embarrassment and humiliation in performance or social situations. This fear often leads to avoidance and/or alcohol, sedative, or drug abuse as attempts at self-medication.

Research (1, 2) has demonstrated that stressful social or performance situations are often accompanied by increased plasma catecholamine levels. An extensive literature, reviewed recently (3), suggests that β-blocking drugs are specifically useful in reducing performance anxiety in normal subjects. Furthermore, Gorman et al. (4) reported, in a small uncontrolled trial, a beneficial effect of the peripherally active β blocker atenolol in patients with social phobia. Interestingly, patients with panic disorder do not seem to respond to β blockers (5) and have normal or decreased β-adrenergic function (6).

The fact that patients with social phobia manifest signs of adrenergic hyperactivity and benefit from β blockers, coupled with findings that epinephrine levels increase during social stress in normal subjects, makes epinephrine infusion of interest as a possible specific provocative agent in social phobia. We hypothesized that epinephrine infusion in doses sufficient to raise plasma epinephrine to levels developed by normal subjects during performance stress experiments might reproduce typical anxiety feelings in patients with social phobia.

METHOD

Eleven outpatients, nine men and two women between the ages of 22 and 37 years (mean, 28 years), who met *DSM-III* criteria for social phobia were studied. The diagnoses were determined by psychiatrists experienced in working with anxiety disorder patients. Exclusion criteria were concurrent major depression, other *DSM-III* anxiety disorders, inability to discontinue psychotropic medication for at least 2 weeks before the study, current alcohol or psychoactive drug abuse, or the presence of any significant medical illness.

After the procedure was explained, all patients gave written informed consent. They were asked to abstain from food, caffeine, and cigarettes for at least 10 hours before the infusion. Throughout the study, the patients were lying in bed. Blood pressure (by intra-arterial transducer) and heart rate (by ECG) were recorded continuously. At 8:30 a.m. an arterial line and a venous line were placed in the subject's arms. Normal saline was infused through the venous line at a rate of 15 cc/hour for 105 minutes (8:45 a.m. to 10:30 a.m.). After the first 45 minutes of saline (at 9:30 a.m.), the subject's head was placed in a clear plastic canopy box, which has been described elsewhere (7), and the baseline blood sample was collected 60 minutes later (0 time). At 10:30 a.m. (0 time) the epinephrine infusion began. The patient did not know when the switch occurred. The epinephrine was administered at a rate of 2.5 μg/minute for 60 minutes. This dose has produced a plasma level of 400 pg/ml (8), a level comparable to that manifested by normal subjects during public speaking (9). At 11:30 a.m. (+60 minutes) the epinephrine was discontinued and normal saline infusion resumed.

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Because only one of the first eight subjects had an observable anxiety reaction and the autonomic changes induced by the epinephrine infusion were modest, the dose of epinephrine was raised to 4 μg/kg of body weight per hour for the last three subjects. The rest of the procedure remained unchanged.

A psychiatrist continuously observed the patient and every 30 minutes administered a 28-item questionnaire, an expanded version of the Acute Panic Inventory (unpublished) that measures the degree of anxiety on a scale of 0 (absent) to 3 (severe); the additional questions on the expanded version are specifically relevant to patients with social phobia. Anxious response was defined as the presence of four *DSM-III* autonomic symptoms for a panic attack and increasing fear of embarrassment or humiliation. Heart rate, blood pressure, and ECG data and spirometric data (average minute volume [calculated as the product of tidal volume and respiratory frequency], oxygen consumption, and CO_2 production) were continuously collected. Five consecutive arterial blood samples were obtained at 0 time (baseline) and every 30 minutes thereafter to measure pH, P_{CO_2}, P_{O_2}, and bicarbonate, epinephrine, and norepinephrine levels. Methods for these assays have been described elsewhere (10).

Paired t tests were used to detect significant within-group changes between 0 and 30 and 30 and 60 minutes. Pearson and Spearman correlation coefficients with Bonferroni correction for 24 coefficients were used to analyze the relationship among four variables (epinephrine level, average minute volume, Acute Panic Inventory score, and heart rate). All p values were two-tailed, and all results are reported as mean±SD.

RESULTS

The epinephrine infusion increased the plasma epinephrine level from 125.7±61.4 to 986.3±494.5 pg/ml in seven of the eight patients who received the low dose (2.5 μg/minute) and from 84.0±51.8 to 868.7±503.6 pg/ml in the three patients infused with the higher dose (4 μg/kg of body weight per hour) of epinephrine. Because of laboratory error, the epinephrine values of one patient who received the low dose were not available.

Only one of the 11 patients experienced any observable anxiety during the infusion, which he described as typical but shorter in duration than his naturally occurring, socially provoked anxiety episodes. His epinephrine level rose from 25 to 1198 pg/ml, a 47-fold increase. His baseline Acute Panic Inventory score was 43; the mean baseline score of the group was 3.2. During the infusion his score rose to 52 at the point of maximum anxiety, which lasted for 20 seconds in contrast to his usual 5-minute anxiety episodes. Eight patients reported transient, uncomfortable physical symptoms such as palpitations, restlessness, paresthesias, lightheadedness, shivering, or weakness, but these symptoms were not accompanied by the usual thoughts of embarrassment or humiliation. Two patients had no symptoms whatsoever during the infusion.

The epinephrine curve in figure 1 shows a steep increase between 0 and 30 minutes, a sustained elevation until the termination of the epinephrine infusion at 60 minutes, and a sharp decline to the baseline level by 90 minutes. The mean plasma norepinephrine levels did not change significantly. The mean Acute Panic Inventory score peaked at 30 minutes and then returned to baseline by 60 minutes (figure 1), even though the epinephrine concentration remained elevated until 60 minutes.

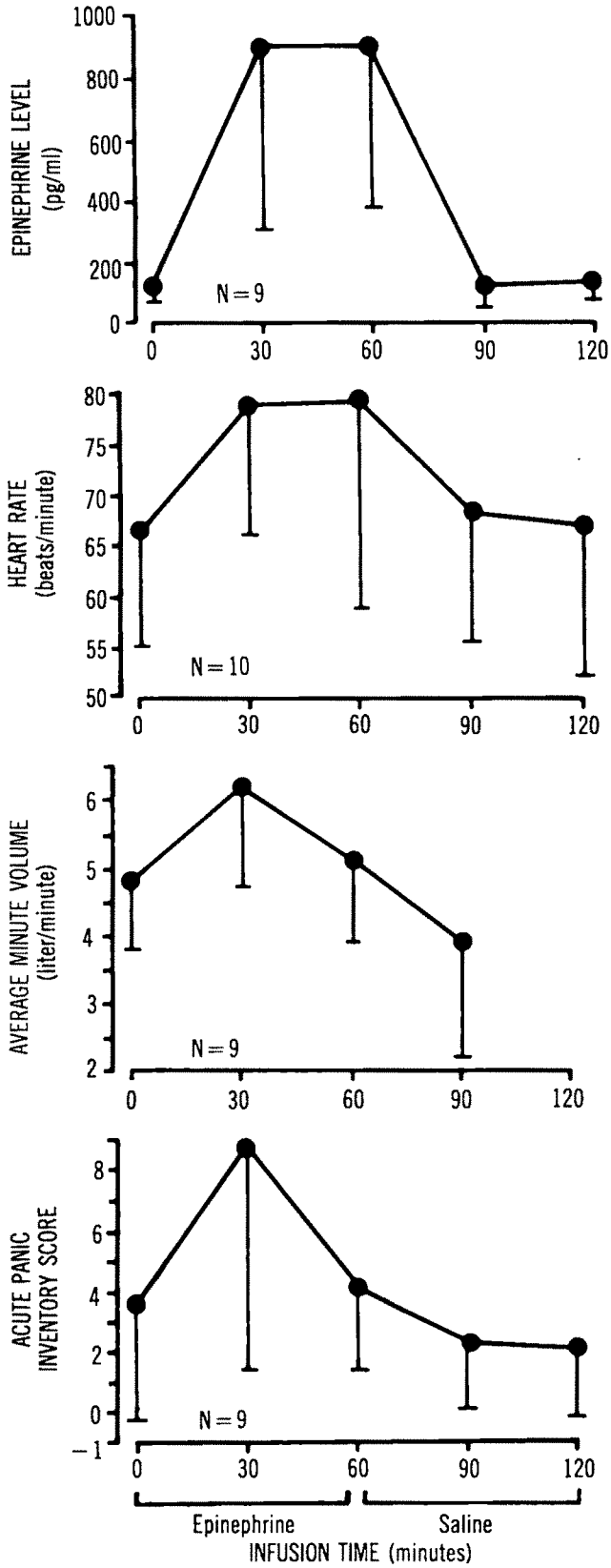
Heart rate and blood pressure changes were in the expected direction. Heart rate increased from 68±11 beats/minute at baseline (0 time) to 79±13 beats/minute at 30 minutes, remained elevated (79±20 beats/minute) through 60 minutes, and then returned to baseline levels (figure 1). The blood pressure changes were similar; the pulse pressure widened from 44 mm Hg (116/72±10/9) at baseline to 61 mm Hg (128/67±14/9) at 30 minutes and continued to widen to 67 mm Hg (133/66±26/7) through the end of the epinephrine infusion.

The average minute volume increased from 4.6±1.1 liter/minute at baseline to 6.2±1.5 liter/minute at 30 minutes, then declined to 5.2±1.1 liter/minute by 60 minutes. This increase in ventilation caused no significant changes in blood gas values.

Of the measured variables, the average minute volume seemed to most consistently follow the Acute Panic Inventory curve. Both peaked at 30 minutes and then returned to baseline. Only the average minute volume and the Acute Panic Inventory scores were significantly correlated throughout the infusion (0 time: $r=0.92$, $df=9$, $p<0.01$; 30 minutes: $r=0.93$, $df=9$, $p<0.01$; 60 minutes: $r=0.97$, $df=9$, $p<0.01$; and 90 minutes: $r=0.98$, $df=7$, $p\leq 0.01$).

With the exception of the one highly symptomatic patient, the total Acute Panic Inventory scores during the infusion were low and in the range observed in panic disorder patients who do not panic during lactate infusion. Nevertheless, an item analysis showed that by 30 minutes there were significant increases over baseline levels ($p<0.05$) in four items: palpitations ($t=-2.19$, $df=10$), general fear ($t=-2.39$, $df=10$), difficulty speaking ($t=-2.19$, $df=10$), and difficulty performing one's job ($t=-2.39$, $df=10$). By the end of the epinephrine infusion (at 60 minutes), only one item (twitching, trembling) was significantly elevated over baseline ($t=-2.63$, $df=10$, $p<0.02$). None of the other items, including the ones specifically referring to social phobia symptoms (feeling embarrassed or humiliated, feeling as if being watched) were rated significantly higher during epinephrine infusion than at baseline.

FIGURE 1. Mean±SD Results of Four Variables Measured in Patients With Social Phobia During and After Epinephrine Infusion[a]



[a]The number of patients on whom data are reported excludes one outlier and reflects occasional data loss on one other patient.

DISCUSSION

At the doses given in this study, epinephrine was not potent in provoking social anxiety attacks in patients with social phobia, despite the mean eightfold increase in plasma epinephrine level. Patients and psychiatrists were in complete agreement in every case about the level of anxiety induced. Although nine subjects reported mild physical symptoms during the epinephrine infusion, only one described his symptoms as resembling his naturally occurring, socially provoked anxiety episodes. His baseline Acute Panic Inventory score was 13 times higher than the mean score, however, and the anxiety episode was much shorter than his usual ones, suggesting that this response was not a true reflection of a naturally occurring attack. The item analysis of the Acute Panic Inventory showed that epinephrine infusion caused increases in some items one would expect to rise during episodes of socially mediated anxiety. It is possible, therefore, that higher or more rapid increases in epinephrine concentration could provoke social anxiety.

In Clutter et al.'s (8) infusion study the 2.5-μg/minute infusion rate produced a mean plasma level of 412 pg/ml and the 5-μg/minute rate raised the level of plasma epinephrine to a mean of 715 pg/ml, peak epinephrine levels that are lower than the ones we obtained. The discrepancy could be explained by assay differences. Our mean baseline values were much higher than Clutter's (113 versus 34 pg/ml), so that the proportional increases in epinephrine levels between the two studies are very similar. In another (unpublished) study from our laboratory, the mean baseline epinephrine values for patients with social phobia and for normal control subjects were not significantly different; therefore, a trait difference is unlikely. Our raising the dose of infused epinephrine from 2.5 μg/minute to 4 μg/kg of body weight per hour did not result in significantly higher peak plasma epinephrine levels, a finding consistent with Clutter's finding that epinephrine increases its own clearance rate.

The average minute volume was the only physiological variable to significantly correlate with the subjective level of anxiety as rated by the Acute Panic Inventory. The psychophysiological literature emphasizes that many physiological measures correlate poorly with rated level of anxiety, the so-called "response desynchrony" (11). Our observation needs to be replicated with larger numbers of patients, but it suggests, in agreement with the findings of Grossman (12), that even in patients with social phobia who do not ordinarily complain of breathing difficulties during anxiety episodes, ventilatory indexes may be better correlates of self-rated anxiety than other physiological variables.

The finding that peripheral autonomic stimulation alone did not reproduce a full social anxiety episode, however, suggests that other, possibly cognitive, factors may be necessary to trigger clinically significant performance or social anxiety. A normal control group and ratings blind to diagnosis would be needed to

ascertain whether patients with social phobia are hypersensitive to exogenous epinephrine.

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Suicide Attempts in Patients With Borderline Personality Disorder

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Among 180 patients with DSM-III *borderline personality disorder, patients with concurrent affective and substance use disorders had a higher rate of serious suicide attempts than other patients. Clinicians should be alert to axis I disorders in assessing suicide potential in borderline patients.*

(Am J Psychiatry 1988; 145:737–739)

Although suicidal behavior is included in the *DSM-III* criteria defining borderline personality disorder, there have been surprisingly few empirical studies documenting the frequency and lethality of suicidal behavior in borderline personality disorder. Stone et al. (1) found a 9.5% rate of completed suicide on 15–20-year follow-up, Akiskal et al. (2) reported a 4% rate during 6–36-month follow-up, and Pope et al. (3) found a 7.4% rate on 4–7-year follow-up. Gunderson (4) reported that 75% of a sample of borderline inpatients had made at least one previous suicide gesture. It has been estimated that 10% of those who attempt suicide eventually succeed.

Borderline personality disorder is frequently concurrent with other psychiatric disorders, and some preliminary studies have suggested that its comorbidity with affective disorder and substance abuse increases the lethality and frequency of suicide attempts. Friedman et al. (5) found that among 76 adolescent inpatients, those who met criteria for both borderline personality disorder and major affective disorder made more lethal and more frequent attempts. In a separate study (6), they found that depressed inpatients with concurrent borderline personality disorder made more numerous and more serious suicide attempts than those with depression alone or depression with any other axis II diagnosis. Crumly (7) reported that of 40 adolescents who had attempted suicide, 24 suffered from major affective disorder, 22 had borderline personality disorder, and most were also substance abusers.

This study was an effort to determine the impact of comorbidity on suicide attempts in a much larger and more diversified sample of borderline patients than previously investigated. We examined comorbidity and lifetime suicidal behavior in 180 hospitalized patients with *DSM-III* borderline personality disorder to determine the degree to which the interaction between borderline personality disorder and affective and substance use disorders influences suicidal behavior.

METHOD

The borderline sample was selected by reviewing the charts of consecutive inpatients between the ages of 18 and 45 years who had been given discharge diagnoses of borderline personality disorder by the treating clinicians. Those who met the *DSM-III* criteria for borderline personality disorder by chart review were entered into the study. A chart review diagnosis of borderline personality disorder was made if it was documented that five of the eight *DSM-III* criteria were characteristic of the patient's long-term functioning before the index admission. In no case did we infer that a symptom or behavior had been present on a

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continuing basis; in each case this information was directly documented in the chart.

Of the 234 charts reviewed, 23% were excluded because of inadequate documentation of the diagnosis of borderline personality disorder. The remaining 180 were included in the study and further reviewed with a 76-item checklist and the *DSM-III* item sets to make *DSM-III* diagnoses for axis I disorders. Again, for all diagnoses, direct documentation of the *DSM-III* criteria was required.

Lifetime suicidal behavior was rated as none, gestures only, or serious attempts. Patients who had made both gestures and serious attempts were included in the latter group.

To establish the reliability of the chart review, 23 randomly selected charts were reviewed blindly by two raters. The kappas for the diagnostic categories were equivalent to those reported for diagnoses based on clinical interviews: major affective disorder, 0.74; dysthymic disorder, 0.46; substance abuse, 0.81; substance dependence, 0.75. For the ratings of the lethality of the suicide attempts, the kappa was 0.72.

The borderline sample was divided into comparison groups according to axis I comorbidity as follows: borderline personality disorder with concurrent affective disorder (major depression, bipolar disorder, atypical depression, atypical bipolar disorder, cyclothymic disorder, or dysthymic disorder), borderline personality disorder with substance use disorder (abuse or dependence of any kind), borderline personality disorder with both affective and substance disorders, borderline personality disorder with neither of these axis I diagnoses. The rates of suicidal behavior were compared with the chi-square statistic.

RESULTS

The 180 borderline inpatients were relatively young (mean age±SD=29.0±6.7 years) and were predominantly white (87%), female (81%), and either single or divorced (87%). Sixty-five percent had concurrent affective disorder, 70% had concurrent substance use disorder, and 43% had diagnoses from both categories. Only 7% had neither diagnosis.

For the entire sample, 19% had no history of suicidal behavior, 32% had made suicide gestures only, and 49% had made serious attempts (see table 1). The borderline patients with both concurrent affective and substance use disorders had a significantly higher rate of serious attempts and a lower rate of suicide gestures than those without either concurrent diagnosis. There was a trend for the borderline patients with concurrent affective disorder alone to have a higher prevalence of serious attempts than those without either concurrent affective or substance use disorder. Fewer of the borderline patients with substance abuse alone had made suicide gestures than those without either axis I diagnosis, but those two groups did not differ significantly in the rate of serious attempts.

TABLE 1. Suicidal Behavior Among Borderline Patients With and Without Concurrent Affective or Substance Use Disorder

Sample	No Suicidal Behavior N	%	Suicide Gestures[a] N	%	Serious Suicide Attempts[b] N	%
Total (N=180)	34	19	57	32	89	49
Borderline only (N=14)	3	21	8	57	3	21
Borderline plus substance abuse and affective disorder (N=77)	10	13	22	30	45	58
Borderline plus affective disorder (N=40)	6	15	14	35	20	50
Borderline plus substance abuse (N=49)	15	31	13	27	21	43

[a]Borderline only versus borderline plus both concurrent diagnoses: $\chi^2=4.38$, df=1, $p<0.05$. Borderline only versus borderline plus substance abuse: $\chi^2=4.59$, df=1, $p<0.05$.

[b]Borderline only versus borderline plus both concurrent diagnoses: $\chi^2=6.51$, df=1, $p<0.02$. Borderline only versus borderline plus affective disorder: $\chi^2=3.46$, df=1, $p<0.10$. Borderline plus both concurrent diagnoses versus borderline plus substance abuse: $\chi^2=2.92$, df=1, $p<0.10$.

DISCUSSION

This study suggests that suicide gestures and serious attempts are common but not ubiquitous in patients with *DSM-III* borderline personality disorder. Comorbidity with affective and substance abuse disorders may increase the risk for more serious suicide attempts in this population. Although the presence of affective and substance use disorders is not necessarily predictive of suicide, it remains true that borderline patients with these axis I disorders demonstrate higher rates of serious suicide attempts. Our results confirm previous findings (5–7) suggesting that the combination of borderline personality disorder and affective disorder carries a high risk for suicidal behavior. In line with previous work indicating that substance abuse increases suicide risk in many populations (8, 9), these data demonstrate a possibly higher suicide risk related to the combination of borderline personality disorder with both affective and substance use disorders. It is crucial that future studies of suicidal behavior in borderline personality disorder take into account comorbidity with axis I disorders. Comparisons of borderline patients with and without affective disorder or substance abuse to patients with these axis I disorders without borderline personality disorder or with other axis II disorders would be the most useful next step in determining the specific contribution of borderline personality disorder to suicide risk.

These results suggest that clinicians should be alert to the presence of axis I disorders in borderline pa-

tients when assessing suicide potential. The axis I syndromes may be easier to treat than the core symptoms of borderline personality disorder, and alleviation of these target symptoms may decrease the risk of suicide. Of interest in this regard is the high rate of suicide gestures in our borderline patients without substance abuse or affective disorder. This raises the possibility that suicide gestures may be related to borderline personality disorder alone and serious attempts may be more subject to the presence of comorbidity.

Although this study suffers from the general limitations inherent in retrospective chart review, the data collection was systematic and comprehensive and reliability was good. The possibility that the presence of serious suicide attempts created a halo effect which resulted in more frequent assignment of affective diagnoses seems unlikely in view of the high rate of serious attempts found in borderline patients with substance abuse but no affective diagnosis.

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Prolactin Response to Tryptophan During Mianserin Treatment

Philip J. Cowen, M.D.

Unlike tricyclic antidepressants and monoamine oxidase inhibitors, mianserin did not increase prolactin response to the 5-hydroxytryptamine (5-HT) precursor tryptophan in nine patients with major depression. Antidepressant drugs apparently produce dissimilar effects on this aspect of brain 5-HT function in depressed patients.

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Several antidepressants have been reported to enhance electrophysiological responses to 5-hydroxytryptamine (5-HT, serotonin) in rodent forebrain. Chronic administration of tricyclic antidepressants, ECT, and the quadracyclic antidepressant mianserin has been shown (1) to increase the inhibitory effect of iontophoretically applied 5-HT in rat hippocampus. The subtype of postsynaptic 5-HT receptor involved in the electrophysiological responses has not been firmly identified but does not appear to be the 5-HT_2 subtype (1, 2).

Determining brain 5-HT function in humans presents difficulties, but neuroendocrine challenge tests offer a possible approach. It is well established that intravenous infusion of the 5-HT precursor tryptophan increases plasma prolactin levels (2), and my laboratory has recently presented evidence (2) that this response is mediated through 5-HT pathways, perhaps involving a postsynaptic 5-HT_1 receptor. Tricyclic antidepressant treatment of both depressed patients (3) and normal subjects (4) increases the prolactin response to tryptophan, and a similar enhancement is seen when depressed patients are treated with the monoamine oxidase inhibitor (MAOI) tranylcypromine (5).

It is clearly of interest to establish whether an increase in 5-HT-mediated prolactin release in humans is common to different antidepressant treatments. We therefore studied the prolactin responses to tryptophan of depressed patients receiving mianserin, an antidepressant drug that does not inhibit 5-HT uptake but antagonizes 5-HT_2 receptors (6). (Mianserin has not been approved for use as an antidepressant in the United States.) In recent studies, it has been shown that acute (7) but not chronic (8) treatment with ritanserin, a 5-HT_2 receptor antagonist, enhances the prolactin response to tryptophan in normal subjects.

METHOD

The subjects were six women and three men who met the *DSM-III* criteria for major depression. After a full explanation they gave informed consent to the study, which was approved by a local ethics committee. They were recruited from a primary care setting; two were inpatients, and the rest were outpatients. Their mean age was 38 years (range, 20–61 years). They were in good physical health and had been free of antidepressant medication for at least 3 months. Four of the subjects were taking benzodiazepines for nighttime sedation; this treatment had started at least 3 weeks before the first tryptophan test and was continued at the same dose until the second test.

The patients were assessed over a period of at least 1 week before mianserin treatment was started. The initial dose of mianserin was 20 mg at night, and this was increased weekly by 20 mg to 60 mg or more on the basis of clinical indications. Before each tryptophan test, the clinical state of the patient was rated by a trained nurse using the 17-item Hamilton Rating Scale for Depression.

Tryptophan testing was carried out on two occasions, once before mianserin treatment and again after 5–8 weeks of mianserin treatment. The preparation of tryptophan for infusion and the procedure for prolactin measurement have been previously described (4). Briefly, after an overnight fast, the first blood sample was taken at 9:00 a.m. After a 1-hour rest period, tryptophan (100 mg/kg of body weight) was infused and blood samples were taken at 15-minute intervals for the next 90 minutes.

Prolactin was measured by means of radioimmunoassay (3). The response to tryptophan was calculated as both the peak change from baseline and the area

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TABLE 1. Effect of Mianserin on Prolactin Responses to Tryptophan in Nine Patients With Major Depression

Patient	Sex	Peak Increase in Prolactin After Tryptophan Infusion (mIU/liter)[a]		Hamilton Depression Score[b]	
		Before Mianserin	Mianserin	Before Mianserin	Mianserin
1	F	493	416	23	4
2	F	334	382	21	5
3	F	155	145	19	9
4	M	30	43	25	12
5	F	205	136	21	8
6	F	75	125	25	20
7	M	57	40	16	17
8	M	262	122	21	15
9	F	0	0	18	14

[a]The mean±SD change in prolactin level was 179±162 mIU/liter before and 157±147 mIU/liter during mianserin treatment.
[b]The mean±SD depression score during mianserin treatment (11.6±5.5) was significantly lower than the score before treatment (21.0±3.0) ($t=4.14$, $df=8$, $p<0.005$, paired t test).

under the curve according to the trapezoid method. These two values were highly correlated ($r=0.98$, $df=16$, $p<0.001$), so in this paper only the change values are given. Statistical comparisons were made with the paired t test (two-tailed).

RESULTS

The mean dose of mianserin used was 71 mg/day (range, 60–120 mg/day), and five of the patients responded, as judged by the criterion of a 50% reduction in Hamilton depression score (table 1). Mianserin treatment did not alter the prolactin response to tryptophan either in the patient group as a whole or in those who improved clinically (table 1). The mean peak change in prolactin level of the patients taking benzodiazepines did not differ from that of the patients who were not.

DISCUSSION

These findings suggest that, unlike tricyclic (3, 4) and MAOI (5) treatment, chronic mianserin administration does not increase the prolactin response to tryptophan. Therefore, repeated antidepressant treatment in humans apparently does not necessarily cause enhancement of 5-HT-mediated prolactin release. However, a number of factors should be considered before this conclusion is accepted.

The patients in this study clearly showed a variation in clinical outcome, and it is possible that mianserin increases the prolactin response to tryptophan only when an effective antidepressant response is obtained. However, there was no relationship between clinical improvement and change in prolactin response after mianserin treatment. Similarly, in patients treated with amitriptyline and desipramine (3), an increase in prolactin response to tryptophan was not necessarily associated with clinical remission.

Four of the nine patients in this study were taking benzodiazepines, which could have interfered with the 5-HT-mediated prolactin responses. In a recent study (9), however, it was shown that while acute diazepam treatment attenuates the prolactin response to tryptophan, continued treatment is associated with a return of the response to normal. Because of this and the fact that benzodiazepine treatment was continued unaltered during mianserin administration, it seems unlikely that an effect of mianserin on prolactin response to tryptophan would be masked by concomitant benzodiazepine therapy.

The lack of effect of chronic mianserin treatment on the prolactin response to tryptophan is consistent with our findings with a more selective 5-HT_2 receptor antagonist, ritanserin (9). A possible explanation for the different effects of chronic mianserin, tricyclic, and MAOI treatment on 5-HT-mediated prolactin release is that, unlike tricyclics and MAOIs, mianserin does not increase the presynaptic availability of 5-HT (2). Whether the difference in the effects of these antidepressant drugs on 5-HT-mediated neuroendocrine responses has clinical implications remains to be determined.

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Adjunctive Alprazolam for Schizophrenia With Panic Anxiety: Clinical Observation and Pathogenetic Implications

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Seven patients with schizophrenia and panic attacks all showed marked improvement of positive and negative schizophrenic symptoms when alprazolam was openly added to antipsychotic medication. Panic attacks may identify alprazolam-responsive schizophrenic patients and may define a distinct pathophysiologic subgroup.

(Am J Psychiatry 1988; 145:742–744)

Two reports (1, 2) have suggested that adjunctive alprazolam may sometimes decrease the positive and negative symptoms of schizophrenia. However, the mechanism of action and which patients will respond are not known. We have suggested (3) that panic anxiety may explain and consistently predict these benefits of adjunctive alprazolam and that panic may contribute to the pathogenesis of schizophrenic symptoms. The present report is a detailed description of seven patients with schizophrenia and panic anxiety who were systematically assessed during open treatment with alprazolam and neuroleptic medication.

METHOD

Seven inpatients with *DSM-III* schizophrenia and panic attacks were treated. Except for the presence of schizophrenia, all seven patients would have met the *DSM-III* criteria for panic disorder. Their neuroleptic doses were held constant for more than 3 weeks before alprazolam was added (table 1) except for one patient, whose haloperidol dose was raised from 40 mg/day to 60 mg/day early in the observation period. The patients received no additional medication. During the first week of treatment, the patients received a dose of 0.25 mg q.i.d. of alprazolam, which was raised to 0.50 mg q.i.d. during the second week; if the panic attacks persisted, the dose was raised by 0.25 mg q.i.d. weekly until they ceased. A stable dose was maintained for 3 weeks; then the alprazolam was tapered over 2 weeks and discontinued for 3 weeks.

A three-psychiatrist team conducted weekly interviews. Positive and negative schizophrenic symptoms were rated on 6-point scales (0 to 5). The Scale for the Assessment of Positive Symptoms (4) includes assessments of hallucinations, delusions, bizarre behavior, and positive formal thought disorder. A total positive symptom score was calculated by averaging the scores from those four categories. The Scale for the Assessment of Negative Symptoms (5) includes assessments of affective flattening or blunting, alogia, avolition/apathy, anhedonia/asociality, and attention. A total negative symptom score was calculated by averaging the scores from those five categories. Panic attacks were assessed by careful review of the occurrence of panic in the preceding week. Attempts at quantifying panic frequency and severity met with unreliable responses.

RESULTS

The five men and two women averaged 11 prior hospitalizations and 14 years of psychosis; the mean duration of current hospitalization was 4 years. All had active psychoses and minimal social and occupational functioning.

Panic history is difficult to elicit and changeable in schizophrenic patients. Most likely, patients are too withdrawn to provide detailed histories, are confused from psychosis, or have severe thought disorder. They typically incorporate panic symptoms into delusional beliefs, usually by attributing them to some external cause. Many patients experience panic attacks as usual, chronic, unremarkable, or untreatable parts of life. Notably, discussion of panic often precipitates an attack. Command hallucinations sometimes instruct patients not to discuss panic. Other patients fear effects on hospitalization status. Finally, panic is sometimes diagnosed as agitation, seizures, asthma, angina, or gastritis.

These seven patients did provide clear initial histories of panic disorder. Notably, their panic attacks

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TABLE 1. History and Response of Schizophrenic Patients With Panic Attacks Who Were Given Adjunctive Alprazolam

Patient	Sex	Reported Age at Onset (years)					Positive Symptoms[a]		Negative Symptoms[b]		Concurrent Medications
		First Panic Attack	First Auditory Hallucination	First Admission	Current Admission	Current Study	Baseline	Treatment	Baseline	Treatment	
1	M	17	21	21	36	45	3.00	1.50	3.40	2.20	Chlorpromazine, 1000 mg/day
2	M	5	20	18	30	36	3.00	1.75	4.20	3.00	Fluphenazine decanoate, 2 cc i.m. weekly
3	M	16	17	20	27	27	3.75	0.25	4.20	1.20	Haloperidol, 60 mg/day
4	M	19	32	16	31	39	2.25	0.50	3.00	1.80	Thioridazine, 400 mg/day
5	F	25	26	16	28	33	2.75	0.75	2.80	1.60	Mesoridazine, 150 mg/day
6	M	17	17	17	35	35	3.00	1.00	4.20	2.00	Chlorpromazine, 1500 mg/day; trihexyphenidyl, 4 mg day
7	F	13	17	13	32	32	2.00	0.75	1.80	0.40	Haloperidol, 90 mg/day

[a]Total score on the Scale for the Assessment of Positive Symptoms (4).
[b]Total score on the Scale for the Assessment of Negative Symptoms (5).

often included paroxysmal fear of loss of control, and some patients attributed previous episodes of agitated, assaultive, or psychotic behavior to panic. Similarly, their panic attacks often included paroxysmal fear of going crazy, and the patients usually reported concurrent abrupt onset or exacerbation of auditory hallucinations. Panic did not appear correlated with self-reported or observed levels of general anxiety. All patients reported that panic attacks had preceded their first hallucinations. Two reported that psychiatric hospitalization had preceded the onset of both panic attacks and hallucinations.

While the effective alprazolam dose for panic cessation was 0.50 mg q.i.d. (six patients) to 0.75 mg q.i.d. (one patient), three patients later had panic attacks while taking these doses. All patients reported recurrent panic attacks after alprazolam withdrawal.

Typically, positive symptoms improved when panic attacks remitted (table 1). From the prealprazolam baseline to the first week of maximum alprazolam dose there was a significant improvement in mean total positive symptoms (paired $t=6.46$, $df=6$, $p=0.001$, two-tailed), hallucinations ($t=6.00$, $p=0.001$), and delusions ($t=5.20$, $p=0.002$) but not bizarre behavior ($t=1.37$, $p=0.220$) or positive formal thought disorder ($t=1.26$, $p=0.253$). These statistics support the clinical observation of substantial and consistent benefit and are not intended to suggest definitive findings. Many patients noticed their own improvement one week and then were anxious, suspicious, sad, or angry a week later. Disinhibited conduct was not noted, and affect sometimes improved with discussion. When alprazolam was tapered, positive symptoms returned quickly, but they remained improved over the baseline level.

Negative symptoms also showed consistent improvement as panic attacks remitted (table 1). From the prealprazolam baseline to the first week of maximum alprazolam dose, there was a significant improvement in mean total negative symptoms ($t=6.10$, $df=6$, $p=0.001$), affective flattening or blunting ($t=3.46$, $p=0.013$), avolition/apathy ($t=2.97$, $p=0.025$), anhedonia/asociality ($t=6.00$, $p=0.001$), and attention ($t=4.58$, $p=0.004$) but only a trend toward improvement in alogia ($t=2.05$, $p=0.086$). These chronic patients showed no short-term improvement in occupational functioning. They did show marked improvements in emotional relatedness and interest in family and social life. Negative symptoms recurred rapidly when the alprazolam was tapered.

DISCUSSION

These pilot data give support to the value of adjunctive alprazolam for patients with *DSM-III* schizophrenia and panic attacks and indicate that controlled trials may have value. Although panic may be common among schizophrenic patients (6), the topic has not been addressed in the literature. This may be because panic in these patients is difficult to elicit and assess, because diagnosis of panic has been of limited therapeutic value, and because panic symptoms seem to pale in importance beside psychosis and severe social impairment.

Notably, these chronic patients showed a substantial improvement in both positive and negative symptoms

that was concurrent with panic cessation. Alprazolam may benefit schizophrenic patients by blocking panic. It is unlikely that the observed benefits were caused by effects on anxiety or akathisia alone. The rapid and global response to alprazolam was similar to that of the responders in a double-blind study (D. Pickar, personal communication, and reference 2). Our patients became more socially related and interactive but retained substantial cognitive pathology. Improved relatedness did allow many patients to more freely discuss and understand their concerns.

Improvement of schizophrenic symptoms coincided with panic cessation, suggesting interrelated pathophysiologies. Although our patients could not provide conclusive histories of the onset of their panic or schizophrenic symptoms, all seven reported that panic had preceded the onset of hallucinations. Since panic may involve activation of CNS autonomic pathways (7), such activation could contribute to the development of a dopamine-mediated, panic-related psychosis in susceptible individuals. This model could be analogous to the schizophrenia-like psychosis and dopaminergic sensitivity induced by chronic amphetamine use (8, 9).

Such a model would also be consistent with our clinical observation of panic-related exacerbation of auditory hallucinations and with the fact that these patients' panic attacks had preceded their hallucinations. Abrupt panic attacks could cause some patients to lose control in impulsive or psychotic behaviors, and negative symptoms could sometimes be due to severe anticipatory anxiety and social avoidance. Controlled studies will be needed to definitively confirm the value of adjunctive alprazolam for schizophrenia with panic attacks.

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Thyroid Indices in Panic Disorder

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The authors compared indices of thyroid function in 26 patients with panic disorder and 26 closely matched control subjects. No significant differences in T_3, T_4, free T_4, thyrotropin, or thyroxine-binding globulin were found between the two groups. Clinical and theoretical implications are discussed.

(Am J Psychiatry 1988; 145:745–747)

Anxiety is a common manifestation of hyperthyroidism (1), and thyroid disorders such as Graves' disease may mimic the clinical presentation of panic disorder (see reference 2 for a review). Instances in which primary thyroid disease is associated with a pathological anxiety state are conceptualized in *DSM-III-R* as an organic anxiety syndrome.

It is less clear from the literature whether panic disorder, in the absence of clinically overt thyroid disease, is routinely associated with physiological disturbances in thyroid function. Several studies have examined the frequency of "abnormal" results on indices of thyroid function in patients with panic disorder, but the findings have varied. Two studies (3, 4) found no abnormalities in routine thyroid-function indices of patients with panic attacks, whereas a more recent report (5) detected an elevation in T_3, T_4, or the free T_4 index in four of 55 patients with panic attacks. These studies (3–5), however, compared test values only with published laboratory norms for their centers and not with values of matched normal control groups, thereby limiting their ability to detect subtle evidence of thyroid dysfunction. Our group (6) recently found reduced thyrotropin (TSH) responses to thyrotropin-releasing hormone (TRH) in some patients with panic disorder, but the precise nature and meaning of this finding is unclear.

In this study, using a group of normal control subjects closely matched in age and sex, we were able to explore the hypothesis that patients with panic disorder might exhibit subtle abnormalities in routine indices of thyroid function.

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METHOD

The samples we studied consisted of 26 patients who participated in ongoing research in the Unit on Anxiety and Affective Disorders at the National Institute of Mental Health, for whom indices of thyroid function were available, and 26 normal volunteers closely matched in age and sex. Patients and normal volunteers with previously documented thyroid disease were excluded from the study. Written informed consent was given by all participants after the procedures had been explained. The mean±SD age of the 26 patients (15 female, 11 male) was 33.9±7.5 years (range =22–52 years); the mean±SD age of the 26 control subjects (15 female, 11 male) was 34.2±8.1 years (range=23–52 years) (t=0.14, df=50, n.s.).

All of the patients and control subjects were interviewed in detail with the aid of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) modified by us for use with patients who have anxiety and affective disorders. All of the patients met the Research Diagnostic Criteria (RDC) for panic disorder, and 17 of them also met the RDC for phobic disorder (agoraphobic subtype). The normal volunteers had no current or past major psychiatric diagnoses. All of the patients and control subjects were judged to be physically healthy on the basis of a complete physical examination, SMA-12, CBC, urinalysis, chest X-ray, and ECG. Both the patients and the control subjects had been free of all psychotropic medications and other medications known to affect thyroid function for at least 10 days before blood sampling for the thyroid function tests. Multiple samples taken over several weeks to several months were available for most of the patients. Rather than use single samples, we averaged the values for the purposes of this study. In most cases, a single sample was available for each control subject.

Routine thyroid indices were measured by using radioimmunoassay for T_3 and T_4, immunoradiometry for thyroxine-binding globulin, equilibrium dialysis for free T_4, and radioimmunoassay for TSH.

We used Student's t test (two-tailed) to compare the

TABLE 1. Thyroid Indices in 26 Patients With Panic Disorder and in 26 Normal Control Subjects

Index	Panic Disorder Patients			Normal Control Subjects				
	Mean	SD	Range	Mean	SD	Range	t[a]	df
T_3 (ng/dl)	144.3	32.1	104–223	140.0	30.5	92–227	−0.50	50
T_4 (μg/dl)	8.8	1.4	6.4–12.0	8.2	1.5	5.8–11.6	−1.42	47
Free T_4 (ng/dl)	1.6	0.4	1.1–2.7	1.7	0.3	1.1–2.6	0.31	47
TSH (μIU/ml)	3.3	0.8	2.0–5.2	3.1	0.6	2.1–4.0	−0.99	44
Thyroxine-binding globulin (μg/ml)	21.4	5.1	14–31	20.9	4.2	17–30	−0.24	25

[a]All differences between groups were nonsignificant.

mean values for the patients and the normal control subjects across all of the thyroid function indices. Levene's F test for homogeneity of variances was used to compare the range and distribution of values between the patients and the control subjects. All p values greater than 0.05 are reported as nonsignificant.

RESULTS

There were no significant differences in measurements of T_3, T_4, free T_4, TSH, or thyroxine-binding globulin between the patients with panic disorder and the normal control subjects (table 1). Similarly, the distribution of values for each of the thyroid-function indices did not differ significantly between the patients and the control subjects (Levene's F test, nonsignificant differences in all cases). When these values were compared separately by sex, no differences emerged.

DISCUSSION

In this study, no differences were found in routine indices of thyroid function between 26 patients with panic disorder and 26 normal control subjects. In interpreting these findings, it should be underscored that patients with previously documented thyroid disease (e.g., Graves' disease, thyroid adenoma) who would have been given a diagnosis of organic anxiety syndrome were excluded from the study. Therefore, these findings by no means obviate the need for thyroid screening in the clinical evaluation of patients presenting with panic attacks (2).

This study does suggest, however, that abnormalities in baseline and peripheral indices of thyroid function are not a requisite biological correlate of panic disorder. This conclusion is supported by our use of a normal control group tightly matched in age and sex and the requirement that the subjects be drug free. We also used a repeated-sampling technique to decrease the likelihood of spuriously abnormal thyroid values. The fact that abnormal T_3, T_4, free T_4, and TSH levels were not found in our panic disorder patients does not preclude the possibility that patients with primary thyroid dysfunction might be predisposed toward the secondary development of anxiety syndromes, even after the correction of the underlying thyroid disease (e.g., hyperthyroidism or hypothyroidism). Furthermore, our findings do not rule out the possibility that hypothalamic-pituitary modulation of peripheral thyroid function may be altered in patients with panic disorder. Future studies that make use of newer immunoradiometric assays with greater sensitivity in the low range of TSH values could, conceivably, detect basal differences in TSH between patients and control subjects. In fact, recent research from our unit indicates that panic disorder may be associated with a blunted TSH response to TRH (6).

We had previously speculated that the blunted TSH response to TRH might reflect a condition of subclinical hyperthyroidism (7, 8) in panic disorder. However, given our new findings presented here, it seems less likely that the blunted TSH response is a consequence of subclinical hyperthyroidism, since we found no tendency for panic disorder patients to exhibit evidence of excess peripheral thyroid hormone levels. It is not known whether the blunted TSH response is the result of a specific disturbance in the hypothalamic-pituitary-thyroid axis or an epiphenomenon of other potential central neurotransmitter abnormalities. Given the myriad ways in which thyroid hormonal changes may affect the noradrenergic receptor system (9) and the suspected abnormalities in noradrenergic function seen in panic disorder (10), this remains a fertile area for future investigation.

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A Carbamazepine Trial in Chronic, Treatment-Refractory Schizophrenia

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Carbamazepine was given to 12 chronic, treatment-refractory schizophrenic patients for 5 weeks. No overall change was found, but four patients significantly improved while eight worsened. Given the paucity of successful treatments for refractory schizophrenia, further study of carbamazepine appears warranted.

(Am J Psychiatry 1988; 145:748–750)

Carbamazepine is gaining widespread use in psychiatry, particularly as an alternative to lithium salts for bipolar patients, but there have been few systematic investigations of its usefulness in treating other psychiatric disorders. Several anecdotal and/or uncontrolled studies (1–3) have suggested that it is effective for violent schizophrenic patients. In a survey of 124 Japanese psychiatrists, the majority (81.5%) reported favorable results with carbamazepine treatment of schizophrenic patients (4). Klein et al. (5) found, in a double-blind study, that carbamazepine plus haloperidol (N=20) was superior to haloperidol alone (N=23) in the treatment of various acutely excited psychotic states, including schizophrenia. We found (6) that addition of carbamazepine to previous neuroleptic therapy produced dramatic success in one refractory patient, but development of hepatitis required discontinuation of the drug. A further adjunctive open trial with six treatment-resistant schizophrenic patients (7) resulted in a clinically modest but statistically significant improvement in scores on the Brief Psychiatric Rating Scale (BPRS). We then decided to conduct a trial of carbamazepine alone with chronic treatment-resistant schizophrenic patients whose histories and clinical evaluations indicated they were free of any neurological disorders.

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METHOD

A protocol to study carbamazepine in treatment-refractory schizophrenia was approved by California's State Committee for the Protection of Human Subjects, and all subjects signed consent forms before their participation. Entered in the trial were 13 treatment-refractory male schizophrenic patients, whose mean age was 33.8 years (range, 25–49). The mean age at the time of first hospitalization was 18.9 years (range, 17–23), and the mean number of years since the onset of psychosis was 14.75 (range, 6–31). The mean length of the current hospitalization was 1.67 years (range, 1–20), and the mean number of prior psychiatric hospitalizations was 11.75 (range, 2–21). The diagnosis of schizophrenia was made by a psychiatrist on the basis of *DSM-III* criteria. Patients with histories of affective illness were excluded from the study.

Determination of treatment resistance was based on documented 1) treatment during the previous 5 years with at least three neuroleptics, from two different chemical classes, for 6 weeks or longer at a minimum dose equivalent to 1000 mg/day of chlorpromazine and 2) failure to respond adequately to antipsychotic therapy during this time, as evidenced by continuous hospitalization or inability to work, poor social relationships, and reports of poor response by contact people during that time. The clinical evaluation included a neurological examination, formal examination for soft signs, EEG with the patient awake (including phobic stimulation and 3-minute hyperventilation), ECG, routine laboratory tests, and BPRS clinical ratings. There were no neurological findings in these patients that indicated any seizure disorder.

Before the study all patients were receiving neuroleptics, which were abruptly discontinued. The subjects entered a 1-week washout period, receiving only placebo tablets, followed by a 5-week clinical trial of carbamazepine. A psychiatrist (J.C.) and clinical psychologist (J.H.), who had established levels of inter-rater reliability and were blind to the procedure, conducted all BPRS ratings. The patients were started on a regimen of 400 mg/day of carbamazepine, which was increased to 600 mg/day by the third day of the trial; the dose was thereafter adjusted on an individual basis to maintain therapeutic blood levels of 6–12

μg/ml. During the washout and carbamazepine trial, the patients could receive chloral hydrate (500–1000 mg) if needed for agitation. Plasma levels of carbamazepine were determined weekly, and blood was drawn weekly for testing of hematopoietic and hepatic function. Clinical change was assessed at baseline, at the end of the washout, and at the end of the drug trial.

RESULTS

Twelve patients completed the entire trial. All of them received 600 mg/day during weeks 2–5 of the drug trial, and all achieved carbamazepine plasma concentrations of 6–12 μg/ml by the second week of the drug trial. One patient was dropped from the study after the first week of carbamazepine treatment because of increasing psychosis, a failure to eat regularly, and an 8-lb weight loss; this patient rapidly improved and resumed eating when neuroleptic treatment was resumed. One-way repeated analyses of variance (ANOVAs) were performed on the BPRS subscale scores for the three periods (baseline, washout, and clinical trial), and the results of these analyses did not reveal significant differences ($F=0.15$, $df=2, 36$, $p>0.05$). Clinical observation suggested, however, that each individual patient either improved or deteriorated during the course of the clinical trial. Therefore, treatment responder (N=4) and nonresponder (N=8) groups were established on the basis of the changes in the patients' BPRS total scores between the washout period and the drug trial. An examination of the total BPRS scores with matched t tests indicated that the responders showed significant clinical improvement after the drug trial ($t=5.196$, $df=3$, $p=0.012$) and the nonresponders showed significant clinical deterioration ($t=4.412$, $df=7$, $p=0.013$). In an attempt to further clarify the symptom specificity of carbamazepine, six BPRS subscales were subjected to matched t tests, and these comparisons revealed that the responders showed significant clinical improvement on the depression subscale ($t=3.323$, $df=3$, $p=0.043$). However, to adjust for the number of t tests completed with the more conservative Bonferroni probabilities, a t value of 5.84 or greater ($p<0.0083$) would have been needed to reach significance at the 5% confidence level. At the completion of the trial, all patients were placed on their previous medication regimens, with the exception of one responding patient, who improved so dramatically that he was immediately discharged from the hospital on a regimen of carbamazepine alone.

Examination of the total number of chloral hydrate doses administered during the course of the carbamazepine trial revealed a nonsignificant trend toward fewer doses among the responders (mean±SD=1.75±2.36) than among the nonresponders (4.75±4.56).

DISCUSSION

Although carbamazepine did not produce an overall effect, we were impressed by a dramatic clinical response in one patient. Further analysis of the data indicated that four patients significantly improved while eight deteriorated during the trial. This divergence in outcome was unexpected in our stable chronic patients and indicates that some schizophrenic patients may benefit from carbamazepine. However, a limitation of this study is the relatively short neuroleptic washout period (1 week), which is too brief to allow for disappearance of all effects of chronic neuroleptic treatment. Future controlled studies should employ a washout period of at least 3 weeks' duration or substitute placebo in responders after treatment to establish the improvement as being clearly drug related.

In our responders, improvement was most notable in the BPRS depression subscale. While this improvement was significant according to a matched t test, it was not significant when a more conservative test was applied. Nevertheless, this finding is not surprising, since carbamazepine appears to possess antidepressant effects (8). Additionally, depressive symptoms may be more susceptible to the greater psychosocial intervention and expectations of response that accompany single-blind trials. It may also be argued that our patients may have been misdiagnosed, but none of our patients had a history of depression or appeared to be depressed. The potential for both antidepressant and antipsychotic activity could make carbamazepine a reasonable alternative to the combination of a neuroleptic with a tricyclic antidepressant for depressed schizophrenic or schizoaffective patients, and this possibility merits further study.

Although one patient was dropped from the study early, none of our patients developed serious side effects from carbamazepine, such as hepatic or hematological changes. However, such results do not indicate that routine monitoring for carbamazepine's well-known medical complications (e.g., hepatitis) should be abandoned. Although we did not encounter any such catastrophic effects during this trial, the trial may have been too short to adequately assess these effects.

We are encouraged by these preliminary findings and are in the process of designing a placebo-controlled trial that would test the antipsychotic efficacy of carbamazepine, both alone and in combination with a neuroleptic.

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Videotape Recording of Inpatient Assaults: A Pilot Study

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Inpatient assaults were videotaped and then characterized by tape reviewers as showing high or low hostility. Over a 2-month period, the videotape reviewers documented more than twice as many high-hostility assaults as were documented by other methods of reporting.

(Am J Psychiatry 1988; 145:751–752)

During a series of ongoing studies of predictors of violence, our group (1) replicated the finding of previous investigators (2) that there is significant underreporting of assaults in psychiatric facilities. While collecting data, we found that reliable characterization of violent events was difficult, since events transpired quickly. It became clear that a more sensitive method of documenting assaults would greatly enhance our efforts, and we therefore considered videotape recordings. To our knowledge, no previous studies of aggression in psychiatric patients have used videotaping.

This paper reports a pilot study in which we used videotape recordings of violent inpatient behavior. It also describes a new method used to characterize and classify assaults. Detection of assaultive events by review of videotapes is compared to detection by conventional methods.

METHOD

The study was conducted in a large metropolitan state hospital, on a 14-bed ward that receives male and female patients who are too assaultive to be managed elsewhere in the hospital. While on the ward, the patients spend most of their waking hours in a large day room.

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A closed-circuit television camera with an 8-mm wide-angle lens and a microphone was placed in each of the four corners of the day room, eliminating all blind spots. Cables connected each of these cameras to a videocassette recorder and monitor screen located in the physicians' office. This instrumentation permitted simultaneous viewing and recording of events in the day room. Recorded segments could then be transferred for storage and review to another videocassette by means of a master videocassette recorder.

The ward staff expressed concern about being videotaped. Therefore, it was agreed that recording would take place only during prearranged hours and that an indicator light would be placed in the nurses' station to alert the staff to the operation of the videorecorders. Further, one of the research physicians would be in the day room during at least 50% of the taping time.

Videotaping took place on weekdays during daylight hours. Videotaped segments ranged from 1 to 5 hours in length; most were taped between 8:00 a.m. and 12:00 noon. Each day the investigators reviewed that day's recordings by playing the four tapes back simultaneously at twice the normal speed. No investigator reviewed the segments of tape recorded while he or she had been in the day room. Each tape segment containing an assault, plus the 5 preceding and 2 subsequent minutes of tape, was then transferred to a master cassette for storage and review.

Assault was defined as an attack on another person, including hitting, kicking, slapping, biting, choking, and throwing objects. The assailant's intent was not included in the definition. However, some authors (3) believe that hostile intent is a necessary component of aggression and that physical contact is not sufficient. We noted that in many events, patients did not seem to mean harm. Therefore, we devised a method to classify events as demonstrating high or low hostility.

First, the victim and the assailant were identified. The assailant was defined as the participant who initiated physical contact. The victim was the recipient of initial contact, even if he or she responded with physical force. Events were rated dichotomously for the following behaviors of the assailant and the victim: 1) gesturing (pointing, fist shaking) or verbal assault (threat) before contact, 2) gesturing or verbal assault after contact, 3) avoidance (running or evading grasp), 4) pursuit, and 5) close proximity after physical contact.

The total hostility score was the sum of 1 point given for the presence of each of items 1–4 and 1 point given for the absence of item 5 for the assailant or the victim or both. Events with a total score of 3 or more (the maximum possible score was 5 points) were classified as high-hostility events. In addition, the day room staff interventions (separation, verbal counseling, and restraint) were noted for each event.

Reliability between raters in identifying who played the roles of assailant and victim and on classification of events as demonstrating high or low hostility was calculated by means of the intraclass correlation coefficient (ICC). The number of high-hostility assaults detected by the videotape reviewers was compared to the number noted in staff reports obtained over the 2-month period during which the tapes were systematically reviewed. Comparisons involved official incident reports, daily entries in the ward journal, and verbal reports obtained by the investigators' interviews with ward staff members each day after taping was concluded.

RESULTS

One hundred twenty-nine hours of tape recorded over 35 weekdays were reviewed. Twenty-four assaultive episodes were videotaped and analyzed. Complete agreement among all three raters in identifying the assailant and the victim in each episode was obtained for 20 of these 24 events (ICC=0.69, df=23, $p<0.001$). All three raters achieved agreement on 16 of the 24 events with respect to the classification of high versus low hostility (ICC=0.62, df=23, $p<0.001$).

The videotape reviewers detected nine high-hostility events as defined by agreement between any two of the three raters. In official incident reports only two of these nine (22%) were noted, while three of the nine (33%) were reported verbally by staff and four of the nine (44%) were recorded in the ward journal. Four of these nine events resulted in staff intervention. Only one resulted in an injury requiring medical attention. Of the 15 low-hostility events, none was reported by any other method, and only one resulted in staff intervention. Videotape reviewers missed one event, which was reported verbally by a staff member as one patient "playfully wrestling" with another.

Low-hostility events typically consisted of brief exchanges in which participants boxed, feinted, or engaged in horseplay. High-hostility events were usually brief exchanges of slaps, kicks, pushes, or punches.

DISCUSSION

We have shown that violent events can be reliably classified into low- and high-hostility groups. We have also shown that nearly all low-hostility and many high-hostility events are not noted by other means of detection and reporting. These findings expand upon those in previous studies of underreporting (1, 2).

The clinical significance of low-hostility assault merits further study. A review of the literature revealed one reference to similar behavior. In his discussion of violence on an adolescent ward, Marohn (4) listed examples of "manageable and tolerable amounts or occurrences of violent behavior," which included one patient bumping another in a table tennis game. Low-hostility assault may represent a mild form of violence—a precursor or provocation for a high-hostility event. However, low-hostility assault may not be related to violence. The lack of mention of most events of this type in any form of reporting by the ward staff supports this conjecture. Continued data collection as well as comparison of the ward staff's ratings of videotapes with those of the present investigators could clarify these issues.

The provision of a signal light and the presence of a physician in the day room may have compromised the staff's and patients' blindness to the taping. The degree to which such compromises affect results can only be determined in better controlled studies.

The study of violent inpatient behavior by videotape review shows promise. Studies in progress at our hospital involve the identification by videotape of specific behavioral antecedents of violent ward events and the detailed characterization of assailants, victims, and nonassaultive control subjects.

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Bulimia in College Women: Incidence and Recovery Rates

Adam Drewnowski, Ph.D., Doris K. Yee, M.A., and Dean D. Krahn, M.D.

In a longitudinal survey of college freshmen, the incidence of bulimia nervosa was 4.2 cases per 100 women per year. Prevalence remained stable (2.9%–3.3%) as new cases were offset by partial remissions. Some women continued bulimic behaviors without meeting the DSM-III-R *criteria.*

(Am J Psychiatry 1988; 145:753–755)

Eating disorders among female students are reported to be increasingly prevalent, reaching alarming proportions on college campuses (1, 2). Bulimia—a syndrome characterized by recurrent eating binges followed by fasting, purging, or vomiting (*DSM-III-R*)—has been reported to affect between 8% and 19% of all university women (1, 3). However, assertions that there is an epidemic of bulimia on college campuses (2) have been questioned (4, 5). Studies based on the more stringent *DSM-III-R* criteria suggest that while bulimic behaviors may be prevalent, only 1.3%–5.0% of college women suffer from a clinically significant form of this eating disorder (4–6). Furthermore, current prevalence estimates are based on one-time survey studies, reflecting the number of probable bulimic individuals in the female population at any one time. To our knowledge, no prospective epidemiological study has yet documented the emergence of new cases of bulimia during the freshman year or assessed the persistence of bulimic behaviors at different points in time.

METHOD

We conducted a two-wave longitudinal survey study (fall and spring surveys) to determine the incidence of bulimia nervosa among female students during the freshman year. The incidence of a disease is defined as the number of emergent cases in the nondiseased population per unit of time. The diagnostic questionnaire, previously validated with clinic patients, included items that approximated the *DSM-III-R* criteria. Women who reported binge eating more than once a week during the previous month, who reported fasting, using laxatives, or inducing vomiting during the preceding month, and who feared losing control during a binge were classified as bulimic. Additional questions addressed weight history, diet habits, and selected demographic variables. Participation was voluntary, and the survey results were confidential. Each respondent was assigned a unique 5-digit code number for both phases of the study, so that an individual's data from the fall and spring surveys could be appropriately linked.

Fall data were based on responses to a mail survey distributed to 2,222 freshman women living in residence halls. Completed questionnaires were obtained from 931 women (a 41.9% response rate). The sociodemographic profile of survey respondents was in every way representative of the entire freshman class. Their mean±SD height was 65.2±2.6 in; their mean± SD weight was 126.4±16.9 lb, and they desired to weigh 117.8±11.8 lb. The spring survey, administered 6 months later to the 931 fall respondents, yielded 599 completed questionnaires (a 64.3% response rate). Spring response rates were the same for women diagnosed as bulimic in the fall (18 of 27, or 66.7%) as for the rest of the sample (581 of 904, or 64.3%), suggesting that no systematic response bias had occurred.

RESULTS

The estimated point prevalence rate of bulimia nervosa in the fall survey was 2.9% (95% confidence interval: 1.9%–4.2%); 27 of 931 freshman women gave responses consistent with a probable diagnosis of bulimia. Six months later, 3.3% of the female respondents (20 of 599) were classified as bulimic (95% confidence interval: 2.1%–5.1%). It should be noted that the frequency of binge eating was assessed over a period of 1 month rather than the 3 months specified by *DSM-III-R*. Although 10.0% of all the women in the fall survey reported binge eating more than once a week, prevalence rates for bulimia nervosa were

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TABLE 1. Characteristics of Female College Freshmen Who Met *DSM-III-R* Criteria for Bulimia Nervosa in Fall or Spring Surveys

Case	Binge Frequency		Loss of Control		Bulimic Behaviors		Professional Contact for Eating Disorder
	Fall	Spring	Fall	Spring	Fall	Spring	
Incident cases							
1	Monthly	Weekly	Yes	Yes	Fasting	Fasting	
2	Monthly	Weekly	Yes	Yes	Fasting	Fasting	
3	Never	Weekly	Yes	Yes	Laxatives	Laxatives	
4	Monthly	Weekly	Yes	Yes	Vomiting, laxatives	Vomiting, laxatives	Yes
5	Monthly	Weekly	Yes	Yes	Vomiting	Vomiting	
6	Monthly	Weekly	Yes	Yes	Vomiting	Vomiting	
7	Monthly	Weekly	Yes	Yes		Fasting, laxatives	
8	Monthly	Weekly		Yes		Fasting, laxatives	
9	Monthly	Weekly		Yes		Fasting	
10	Weekly	Weekly	Yes	Yes		Fasting	
11	Weekly	Weekly	Yes	Yes		Laxatives	
12	Monthly	Weekly	Yes	Yes		Vomiting	
Chronic cases							
1	Weekly	Weekly	Yes	Yes	Fasting	Fasting, vomiting	Yes
2	Weekly	Weekly	Yes	Yes	Fasting	Vomiting	
3	Weekly	Weekly	Yes	Yes	Fasting, vomiting	Vomiting	Yes
4	Weekly	Weekly	Yes	Yes	Fasting, vomiting, laxatives	Vomiting	Yes
5	Weekly	Weekly	Yes	Yes	Fasting, vomiting, laxatives	Fasting, vomiting, laxatives	
6	Weekly	Weekly	Yes	Yes	Vomiting, laxatives	Fasting, vomiting, laxatives	
7	Weekly	Weekly	Yes	Yes	Laxatives	Laxatives	
8	Weekly	Weekly	Yes	Yes	Vomiting	Fasting, vomiting	
Cases in partial remission							
1	Weekly	Monthly	Yes	Yes	Fasting		
2	Weekly	Monthly	Yes	Yes	Fasting		
3	Weekly	Weekly	Yes	Yes	Fasting		
4	Weekly	Monthly	Yes	Yes	Fasting		
5	Weekly	Monthly	Yes	Yes	Laxatives		
6	Weekly	Weekly	Yes	Yes	Vomiting, laxatives		
7	Weekly	Monthly	Yes	Yes	Vomiting		
8	Weekly	Monthly	Yes	Yes	Vomiting, laxatives	Vomiting	Yes
9	Weekly	Monthly	Yes	Yes	Fasting, vomiting, laxatives	Vomiting	
10	Weekly	Monthly	Yes	Yes	Fasting	Fasting, vomiting, laxatives	Yes

sharply reduced as additional *DSM-III-R* criteria were included (5).

Contrary to expectation, the fall and spring bulimic respondents were generally not the same women. Twelve new cases were found among the 20 bulimic respondents in the spring survey, representing a 2.1% incidence rate during the 6-month period (95% confidence interval: 1.1%–3.6%). Although all of these women had reported either binge eating, fasting, purging, or vomiting during the fall, all of them had failed to meet *DSM-III-R* diagnostic criteria for bulimia nervosa at that time. As shown in table 1, diagnosis of bulimia nervosa in the spring survey was based on increased frequency of binge eating (10 of 12) and emergence of fasting (four of 12) or use of laxatives (three of 12).

Spring data were also obtained for 18 of the 27 women who had been identified as probable bulimic respondents in the fall survey. Eight of 18, or 44.4%, were still classified as bulimic (chronic cases). These women continued binge eating weekly or more often and reported fasting, vomiting, or use of laxatives (see table 1). The remaining 10 women (55.5%) no longer fulfilled the diagnostic criteria for bulimia nervosa, and some showed evidence of spontaneous—if only partial—remission. The most common improvements were reduction in binge frequency (eight of 10) and cessation of fasting (five of 10), laxative use (four of 10), or vomiting (two of 10).

DISCUSSION

The probable incidence of bulimia nervosa among the freshman women was 2.1% per 6 months, or 4.2 new cases per 100 women per year. As far as we know, this is the first estimate of the true incidence of this disorder on a college campus. Since emergent cases were offset by partial remissions, prevalence rates remained stable between the fall and the spring surveys.

The vital distinction between bulimic behaviors and the clinically significant syndrome of bulimia nervosa was noted in a previous study (*5*). Since the clinical course of the syndrome is exacerbation and remission, some women fulfilled the *DSM-III-R* criteria only during the fall or the spring survey. In contrast, bulimic behaviors were typically long-lasting. Binge eating, fasting, or purging almost invariably predated by 6 months the onset of bulimia and sometimes continued after incomplete recovery. Virtually all respondents continued to report loss of control during a binge.

As shown in table 1, only a minority of the bulimic college women sought professional help for an eating disorder during their first 6 months on campus. Reported improvement occurred largely in the absence of professional intervention. However, the categorical diagnosis of bulimia provides a poor indication of the development of eating disorders or the dynamics of recovery in a nonclinical sample. A continuous scale might better assess the extent of pathological efforts at weight control and their changes with time. Further prospective studies are also needed to examine the role of social and psychological risk factors in the development of eating disorders in college women.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

SUBSTANCE ABUSE

Betty: A Glad Awakening, *by Betty Ford with Chris Chase. Garden City, N.Y., Doubleday & Co., 1987, 217 pp., $16.95.*

From its earliest days a goal of the National Institute of Alcohol Abuse and Alcoholism has been to destigmatize alcoholism. The idea was that if problem drinkers were less embarrassed by their problem they would be more willing to get help. Celebrities recovering from the problem were recruited to go on the lecture circuit to talk about it.

No celebrity has been as effective in this effort as former First Lady Betty Ford. More or less dependent on alcohol, pain pills, and tranquilizers for 30 years, she had the eventual good fortune to have two excellent physicians (maybe the best there are) as her doctors and a large supportive family. At the age of 60, she checked into the Long Island Naval Rehabilitation Unit and came out 28 days later not cured perhaps (Alcoholics Anonymous rejects the notion of cure) but, in her words, clean. Since then she has been helping others to get clean.

Mrs. Ford travels as much as her husband, making speeches. She opened a treatment center in Palm Springs. And she has written two books. The first (1) was mainly about life as a politician's wife, with a chapter added grudgingly about her problem with pills and alcohol. The second book, reviewed here, is mainly about pills and alcohol.

She talks about her own drinking:

> I think of my first trip to Europe, in 1956, and a train from Italy to Austria, and Jerry and me drinking our whiskey out of paper cups. We iced it with fresh snow we scooped up off the windowsill of our compartment and laughed ourselves to sleep . . . . I think of vacations, christenings, rituals, festivals, of lunch drinks and dressing drinks while we were preparing to go out, and nightcaps before bed . . . . Drinking was the way we relaxed, a way we celebrated, and it was good until it went bad. If you are not alcoholic, it doesn't have to go bad, but I am alcoholic.

She can now talk about being alcoholic. This was perhaps the hardest thing about her treatment, getting herself to use the word. William James (2), having listed all the excuses alcoholics have for drinking, said that the ability to name the problem was crucial to recovery: "If through thick and thin he holds to it that this is being a drunkard and is nothing else, he is not likely to remain one long," James wrote. "The effort by which he succeeds in keeping the right *name* unwaveringly present to his mind proves to be his saving moral act" (p. 565). Betty Ford finally accepted the right name, but as Drs. Cruse and Pursch would testify, it was a struggle, mainly because of the pills. Betty had a pinched nerve in her neck and a bad back and was given pain pills. She was anxious about this or that—including a mastectomy—and was given tranquilizers. She couldn't sleep and was given sleeping pills. She took pills and then drank and found it took forever to get dressed. She was a zombie at dinner parties.

For a long time people, including her husband, blamed the pills. Her drinking seemed so social. Clearly, pills were part of the problem, but she now believes that alcohol was the main problem.

Much of this book is about the Betty Ford Center, dedicated in 1982 with Bob Hope, George Bush, and other celebrities looking on. Since then it has become the rehabilitation unit for celebrities. A celebrity checks in, checks out, and holds a news conference. For this group, at any rate, the stigma seems to have vanished entirely.

Hundreds of rehabilitation units have opened in the United States in the past few years, most of them modeled after the Betty Ford Center, which in turn was modeled after the Hazelden ("Hazel's den") Center in Minneapolis. The success of these units depends on thousands of people admitting that they have a drug or alcohol problem. Clearly some of the embarrassment is gone.

For example, a Midwest congressman running for office recently was accused by his opponent of being absent too much from his post in Washington. The congressman responded indignantly, saying that his opponent obviously knew the reason that he had been absent so much was that he was being treated for alcoholism. Here was a man who would rather be considered alcoholic than lazy. This has to represent a certain change in community attitudes.

By the example of her own recovery, Betty Ford has been a source of hope and comfort for many. Her new book can be recommended to patients and their families.

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DEPRESSION

Differential Therapy of Depression: Possibilities and Limitations, *edited by H. Hippius and N. Matussek, with the assistance of M. Schmauss. Basel, Karger, 1986, 229 pp., $103.50.*

This text is the second volume of the series Advances in Pharmacotherapy, whose goal is to provide the physician with new information on the treatment of patients with depression. With this theme in mind, I reviewed the book with the intent to determine the value of the volume to the

clinician with respect to the day-to-day treatment of depressed patients.

The book is divided into five sections: Clinical and Therapeutic Aspects, Biochemical and Endocrinological Aspects, Clinical-Neurophysiological Aspects, Internal Aspects, and Pharmacological Aspects. The papers in the volume were presented at the Third Symposium on Fluvoxamine. Thus, the majority of the papers involve research done in part with the antidepressant fluvoxamine.

One consistent theme is obvious in the seven papers presented in the clinical and therapeutic aspects section of the monograph. It has been hypothesized that depression can be biochemically dichotomized into serotonin-deficient and norepinephrine-deficient subtypes. If this hypothesis is true it follows that the serotonin-deficient depressions ought to be treated with serotonin-agonist drugs, such as fluvoxamine, and the norepinephrine-deficient depressions ought to be treated with norepinephrine-agonist drugs, such as desipramine. The crossover studies described in this section have found these treatment practices to be unsuccessful. However, the chapter by Pichot, "Clinical Nosology and Therapy of Depression," offers the clinician a superb summary of how to clinically determine from the patient's presentation of symptoms the antidepressant treatment of choice of ECT, tricyclic antidepressants, or monoamine oxidase inhibitor antidepressants.

The book's unit on the endocrinological aspects of depression contains a very useful chapter that discusses the sensitivity and specificity of the dexamethasone suppression test. The clinical-neurophysiological aspects section devotes its attention to discussions of the validity of sleep architecture as a legitimate biological marker for the diagnosis and treatment of depression. The authors present data suggesting that the increase in REM sleep latency produced by antidepressant drugs does not differentiate between responders and nonresponders. The two papers presented in the internal aspects section are devoted to demonstrating the lack of cardiotoxicity and hepatotoxicity of fluvoxamine. Finally, the section on pharmacological aspects contains five papers that use as their central theme the mechanism of action of the antidepressant drugs. The authors attempted to reconcile how fluvoxamine can have antidepressant activity in spite of the fact that it is unable to produce down-regulation of β-adrenergic receptors.

Since it was the goal of this volume to provide the clinician with new information in the treatment of depression, it would seem that this book may be of considerably limited value. Other than Pichot's chapter, the text is restricted to a discussion of the clinical use and basic pharmacology of the antidepressant fluvoxamine, which has not yet been released in the United States.

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Essential Papers on Depression, *edited by James C. Coyne. New York, New York University Press (Columbia University Press, distributor), 1986, 492 pp., $50.00; $22.50 (paper).*

Essential Papers on Depression is the most recent volume in the series Essential Papers in Psychoanalysis. Other topics in the series have included borderline disorders, object relations, and narcissism. This volume consists of previously published papers and book chapters detailing different theoretical perspectives on depression, including psychodynamic, cognitive and behavioral, interpersonal and social, and biomedical approaches. Interestingly, less than one-third of the present volume is devoted to the psychoanalytic perspective on depression. The editor, James C. Coyne, a depression theorist and researcher, provides the reader with an introduction to the phenomenology of depression and a brief commentary regarding the historical or current context of each of four major approaches to the study of depression.

The primary contribution of a collection of previously published papers is that the student has ready access to major statements on a particular topic. *Essential Papers on Depression* succeeds in part with the classic contributions of Abraham and Freud to the psychodynamic perspective and the theoretical contributions of Lewinsohn, Seligman, Beck, and Rehm to the behavioral and cognitive perspectives. Coherence was less noticeable in the section entitled Interpersonal and Social Approaches. Coyne's own contribution regarding interpersonal disturbance in depression and George Brown's discussion of a three-factor model of depression are successful. However, the contribution by Billings and Moos seems more of an attempt to integrate a large body of psychosocial research than a clear theoretical statement about the etiology of depression. Becker, a sociologist, seems more interested in ridiculing the psychoanalytic perspective than developing a clear theoretical statement of his own.

Despite the enormous research interest in the biological and genetic underpinnings of depression, relatively little space is devoted in this book to the biomedical approaches (chapters by Winokur, Dunner, and Baldessarini). Moreover, two of the papers that Coyne selected were originally presented at a scientific meeting and were, of course, rather limited in their scope. This section would have been much more satisfying had comprehensive chapters by the same authors been commissioned to represent adequately the breadth of theorizing in the biomedical approach to depression. Perhaps the psychoanalytic thrust of the Essential Papers series militated against more adequate coverage.

This volume would be of most interest to individuals desiring an introduction to the psychosocial perspectives on depression. Although Coyne provides some commentary on each major section, it is more descriptive than critical. There is little that is new for depression researchers and clinicians who treat depression. Finally, the production of this volume is marred by sloppy proofreading; there are numerous typographical errors throughout the book.

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PSYCHOTIC DISORDERS

The Clinical Roots of the Schizophrenia Concept: Translations of Seminal European Contributions on Schizophrenia, *edited by John Cutting and Michael Shepherd. New York, Cambridge University Press, 1986, 238 pp., $54.50.*

It is not unusual to find references to Kraepelin, Eugen Bleuler, or Schneider's works in many of the current papers on schizophrenia appearing in the most credited, up-to-date psychiatric journals. These are not merely historical quotations; rather, they are used as main points of reference in psychopathological discussions.

This would suggest that the psychopathology of schizo-

phrenia and, by extension, the research on the whole field is still linked to its roots in the European tradition from the turning of the twentieth century. In that context, Cutting and Shepherd's book is to be welcomed as useful and timely.

The volume is a collection of translations of classical texts about the psychopathology of schizophrenia. It is structured in two parts: German-language and French-language contributions. The first section includes a chronologically ordered selection starting from the first account of dementia praecox by Kraepelin in 1896, which has never been translated into English before, to a closing review of the state of German psychopathology in the 1970s by W. Janzarik. Otto Gross's definition of "dementia sejunctiva," Stransky's concept of intrapsychic ataxia, and Eugen Bleuler's article introducing the term "schizophrenia" for the first time are some of the selected texts.

The second section includes some classical masterpieces such as the description of the misinterpretative delusional states by P. Sérieux and J. Capgras, Clérambault's definition of erotomania, and an extract from the work of P. Chaslin that illustrates the similarity of his concept of discordant insanity to the Germanic concept of dementia praecox.

The young student of schizophrenia, born around the time chlorpromazine was discovered, will probably be surprised to find out how insightfully and deeply the masters of the past went into the nature of schizophrenia. The clinical descriptions, some of them of single paradigmatic cases, are often a delight to read and depict syndromes whose clinical richness is scarcely seen today.

The book has also a practical value for the current researcher on schizophrenia in that it constitutes a pool of observational and theoretical data, excellent to stimulate current thinking in fields like nosology, attention disorder, formal thought disorder, hemisphere imbalance, and schizoid personality. Some of the texts, like Kleist's 1930 paper on thought and language disorder, are amazingly up-to-date in anatomical precision and theoretical formulations. In the introduction the editors point out some of the interesting connections between the old ideas and their modern counterparts. Each text is preceded by a biographical note on the author, which is quite illustrative and interesting but too brief.

Although the clinical method is the common thread in the selection, the spectrum covered is wide. Authors like L. Binswanger, E. Minkowski, and J. Lacan are included.

Overall, the book, probably unprecedented in its conception, seems quite timely now when psychiatry is increasingly biologically oriented and needs to hold on to a rigorous clinical approach.

The purpose of the editors—"to acquaint contemporary students of schizophrenia with the seminal works on schizophrenia"—would have been better accomplished had the selection included such important names in the field as K.L. Kahlbaum, E. Kretschmer, K. Jaspers, K. Schneider, B.A. Morel, and H. Claude as well as representatives of the Russian school. Some of this work has already been translated into English, but their exclusion from this book is probably due to space limitations. If this is so, a second volume of this valuable book including other important contributors to the concept of schizophrenia would be warmly welcomed.

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Handbook of Studies on Schizophrenia, Part 1: Epidemiology, Aetiology and Clinical Features, *edited by Graham D. Burrows, Trevor R. Norman, and Gertrude Rubinstein. Amsterdam, Elsevier, 1986, 228 pp., $72.25.*

Handbook of Studies on Schizophrenia, Part 2: Management and Research, *edited by Graham D. Burrows, Trevor R. Norman, and Gertrude Rubinstein. Amsterdam, Elsevier, 1986, 313 pp., $92.50.*

Interest and research in schizophrenia have increased appreciably in the past few years, although many fundamental questions regarding this complex and etiologically elusive group of disorders remain unanswered. There is an ever growing number of edited books on schizophrenia. Many of these volumes contain chapters on similar topics written by familiar experts. Given the plethora of such easily replaceable books, one comes to view any new edited book on schizophrenia with some skepticism. It is against this background that the two-part *Handbook of Studies on Schizophrenia,* edited by Drs. Burrows, Norman, and Rubinstein, comes as a breath of fresh air. All three editors are from the Department of Psychiatry of the University of Melbourne in Heidelberg, Australia. The *Handbook* is an attempt to provide a concise overview of what the editors consider some of the major areas of interest in schizophrenia and to summarize the current state of knowledge in these areas. The book is remarkable because of several unusual topics covered as well as its well-organized and carefully edited individual chapters.

Part 1 contains chapters on such usual subjects as epidemiology, genetic studies, phenomenology, diagnosis, and prognosis. These chapters stand out in comparison with similar chapters in some other books by virtue of their brevity and readability. The introductory chapter by Manfred Bleuler is refreshingly personal; he gives both positive and negative sides of his "credentials" for surveying the literature on schizophrenia. Topics not usually covered, such as schizophrenic art, language in schizophrenia, sexual dysfunction in schizophrenia, schizophrenia and the puerperium, and cross-cultural studies in schizophrenia, form separate chapters in *Part 1.* One particularly well-written chapter reviews depression in schizophrenia. The articles by Drs. Carpenter, Crow, Johnstone, Zubin, Roth, and Flor-Henry are, as would be expected, highly readable.

Some of the chapters present summaries of the literature in the different areas cited, highlight recent and past findings in a semidogmatic vein, and then go on to speculate about future possibilities. Others review the existing data and conclude that, in reality, relatively little is known about a number of important issues. The combination of such styles (particularly the latter) in a reference text such as this is valuable, since it gives the reader not only an overview of the relevant literature in disparate aspects of schizophrenia but also an accurate sense of some of the limitations in our knowledge about this heterogeneous brain disease.

Part 2 also contains some highly readable overviews on management and research, although this volume may appear a little less exciting than *Part 1.* Probably the most interesting section is entitled The Consumer's Viewpoint, which includes two chapters by the director and the president of the Schizophrenia Fellowship of Australia, an organization of patients with schizophrenia and their close relatives. One chapter contains results of a survey based on questionnaires completed by patients about their illness and its treatment. This should be of interest to psychiatrists and other caregiv-

ers. Subjects such as pharmacotherapy, psychotherapy, family therapy, behavior modification, central and peripheral monoamines, and positron emission tomography (PET) scanning are also covered well in *Part 2*.

Each volume ends with an overview written by the editors. This, in addition to the organization of individual chapters, speaks well for the editorial work.

On the negative side, it is a little surprising that subjects such as childhood schizophrenia, late-onset schizophrenia, or neuropsychological performance of schizophrenic patients are not covered. Also, a few chapters fail to review the literature adequately. For example, the chapter on tardive dyskinesia makes no mention of the APA Task Force recommendations on neuroleptic use (1).

Overall, the book has many more pluses than minuses. It is recommended to clinicians, researchers, and students of psychiatry. This *Handbook* represents a well-designed and accomplished overview of some of the important areas in the study of schizophrenia. The editors have been successful in orchestrating a concise and readable compendium that should appeal to professionals at different levels of training and experience who are interested in a multimodal reference on one of the most studied yet least understood brain disorders.

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The Delusional Misidentification Syndromes, *edited by G.N. Christodoulou. Basel, Karger, 1986, 148 pp., $41.75.*

Most psychiatrists have heard of the Capgras syndrome but few of us have seen a convincing case. This book does a service by reminding us of the condition and by emphasizing that it is only one of a number of misidentification disorders which, although apparently rare, are of considerable clinical interest and may be of potential value in research into localization of recognition and identification mechanisms in the brain. Unfortunately, having given us a reminder, the book does little more, and it is clear that this is due to a serious lack of factual data about the condition it describes.

Each chapter is really a self-contained article on some aspect of the topic. There is little attempt at editorial cross-reference apart from a short introduction. There is a lot of unnecessary repetition and a good deal of unconvincing theorizing. The authors are eminent and well-informed, but most of them are scratching around in pretty thin soil, and the only outstanding contribution is that by Anthony B. Joseph of Harvard, who provides a short, sharp, commonsense review of the range of misidentification syndromes, of the more reproducible investigations that have been reported, and of the possible underlying central nervous system abnormalities.

The book indicates that there is still controversy as to whether misidentification syndromes are really syndromes or epiphenomena of other psychiatric or neurological disorders. Certainly many of the case descriptions in the literature indicate that misidentification phenomena are often secondary to another condition. The proportion of recognizable underlying neurological pathologies has risen as investigative skills have sharpened, yet some psychiatrists still persist with psychodynamic explanations that are now becoming increasingly quaint.

Why does every psychiatrist know about the Capgras phenomenon when it is so rare? Probably because its symptoms have cropped up as themes in mythology and literature throughout the ages. Most people are intrigued by tales about doubles, substitution of one person by another, misidentification, changelings, and many other connected topics. The illness may be rare but the features of the phenomenon, in one form or another, strike chords within us all and may represent some atavistic element in our mental functioning. Several chapters deal with speculations of different sorts along these lines.

The book can be read quickly, and it should be available in libraries, but I would not recommend it for personal purchase. It represents the "state of the art" in 1986. Joseph's chapter gives encouragement that we might look forward to a "state of the science" volume in the coming decade.

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Psychotherapy and the Paranoid Process, *by W.W. Meissner, S.J., M.D. Northvale, N.J., Jason Aronson, 1986, 417 pp., $40.00.*

This is a difficult book to review. There is so much in it to both commend and criticize that one feels a little uncertain as to how to proceed. To begin with, Dr. Meissner provides a theory of psychological development, the paranoid process, which he argues is a "general, even universal, process that comes into play in many aspects of human experience and personality functioning." More specifically, the theory proposes that a set of mental mechanisms are critical in the formation of the individual's psychic world and his or her experience of self. These mechanisms are introjection, the preservation of a lost object intrapsychically through "internalization"; projection, the externalization of components of introjections; and, finally, the paranoid construction, the cognitive reorganization of the introjections and projections. The inclusive term "paranoid process" is not intended to simply define a pathological process. It refers to those normal psychological mechanisms by which the mind develops into a complexly differentiated and integrated "organ" of perception, memory, identity, volition, etc. In instances of psychopathology these processes miscarry and help to elucidate different manifestations of behavior such as schizophrenia, paranoia, and personality disorders.

Part one of the book focuses on the elaboration of the conceptual framework, part two applies the idea to major forms of pathology, part three is devoted to diagnosis and treatment of patients, and part four has chapters on adolescent development, suicide, addiction, and aging.

What Meissner actually attempts to do is to use the defense mechanisms of introjection and projection as core concepts with which to integrate ego psychology, self psychology, and object relations theory. This is currently a favorite pastime among systematic thinkers in psychoanalysis, and Meissner's efforts are commendable and merit close attention. Meissner also integrates findings from nonanalytic researchers, which is unique in a book with this psychoanalytic bias. He is knowledgeable about phenomenology, diagnosis, neurophysiology, and cognitive psychology. However,

his commitment to ego psychology and its outdated concepts of libidinal theory with energic concepts of cathexis and countercathexis is a little bit too central for my taste, but in fairness to Meissner he is fair to the other schools of psychoanalytic thought.

The result is interesting reading for one who is knowledgeable about psychoanalysis. The book will be tough going for others. This is a major loss for the author because it restricts him to a smaller audience than he deserves. I doubt, for example, that many cognitive therapists will make it far enough into the book to evaluate Meissner's use of their concepts. The same can be said about his neuropsychological and pathological formulations. In particular, I don't think that many residents interested in learning psychotherapy will easily get through the opening section. This is a pity because the theory is accompanied by excellent clinical presentations.

The 28-page chapter on the psychotherapeutic schemes is wonderful; it is the best brief description of psychotherapy that I've read in a long time. It is a personal creative resynthesis of familiar ideas that is stimulating and refreshing. Similarly, Meissner's chapter on the borderline personality (yes, another chapter on borderline personality) has the same touch. An additional merit to his "reviews" is their inclusiveness. Meissner picks over the familiar sources on the borderline personality such as Kernberg, Masterson, Gunderson, Grinker, and Adler but includes other, less familiar contributors, especially those from the British object relations school such as Winnicott, Fairburn, and Guntrip, and integrates their work in a clinically useful way. I found myself noting references that were unfamiliar, that were 20–40 years old, and that I wanted to read.

The best audience for this book will be nondoctrinaire psychodynamically sophisticated therapists. They will dismiss the jargon, enjoy the intellectual excitement of the attempt at synthesis, and delight in the clinical relevance of the ideas and examples. Nonpsychoanalytic psychotherapists will too quickly reject it as too psychoanalytic, and orthodox psychoanalysts will get lost in exposing the "deviations" from acceptable theory. I am uncertain whether to encourage these readers to persevere with tolerance or to encourage Dr. Meissner to write a more general clinical text that is less burdened with a need to integrate existing theories and would permit his own originality and clinical contribution to clearly emerge.

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AGING AND ITS DISORDERS

The Loss of Self: A Family Resource for the Care of Alzheimer's Disease and Related Disorders, *by Donna Cohen, Ph.D., and Carl Eisdorfer, Ph.D., M.D. New York, W.W. Norton & Co., 1986, 359 pp., $19.95.*

This is a superb resource both for clinicians and for the family members of Alzheimer's disease victims. Based on their long clinical and research experience at the University of Washington and elsewhere, the authors have created an extremely useful volume dealing with the vicissitudes of Alzheimer's disease and related dementias. The book begins with a review of the diagnosis of dementia and what the term means, not only in a medical sense but in a more personal and existential sense as well. In this context, *The Loss of Self* is in the genre of Oliver Sacks's *The Man Who Mistook His Wife for a Hat* (1). Both are detailed and beautiful accounts not only of the clinical phenomenology of neuropsychiatric disease but also of what the experience of being afflicted, of losing self, is really like.

The authors discuss both personal and family reactions to the diagnosis of dementia and describe ways in which families can set goals after the diagnosis, ways of caring—particularly at home—and ways of coping with the stress of caring. This last is particularly well done. The authors also discuss issues related to rehabilitation, the choice of a nursing home, facing death and dying, what we know about the causes of dementia, and the economic aspects of caring. The text is accompanied by four detailed appendixes dealing with self-help groups, national organizations on aging, sources of help, and different legal and financial issues.

Throughout the volume, Drs. Cohen and Eisdorfer cite individual case examples to illustrate how their patients have reacted to the diagnosis of dementia and how they have coped with it. These examples show how the families of Alzheimer's victims have developed creative and loving ways of coping with an insoluble dilemma. The case vignettes are often moving as well as informative and convey what Alzheimer's disease is about at an existential level. Both clinicians and families will learn a great deal about the disease from these vignettes. Their utility to families probably cannot be overestimated.

Another valuable aspect of this volume is that it portrays the many ways that mental health professionals can be and are helpful to victims of Alzheimer's disease and to their families. In this sense, the book goes a long way toward reestablishing the legitimacy of psychiatry's claim to a valid and useful clinical role in dementia. My sense is that this book will be a standard practical reference in the field for many years to come.

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Clinical Disorders of Memory, *by Aman U. Khan. New York, Plenum, 1986, 272 pp., $35.00.*

Rehabilitation of Memory, *by Barbara A. Wilson. New York, Guilford Press, 1986, 259 pp., $30.00.*

Disordered memory is again becoming a matter of central interest to psychiatrists. Perhaps this reflects the resurgence of neuropsychiatry or the recent emergence of geriatric psychiatry as a distinctly recognizable field. Certainly the involvement of many psychiatrists in pharmacotherapeutic trials with patients suffering from Alzheimer's disease has required more than passing knowledge of memory tests and other cognitive assessment procedures.

Thus, Aman Khan's *Clinical Disorders of Memory* is an ostensibly well-timed addition to Plenum's Critical Issues in Psychiatry series. Barbara Wilson's *Rehabilitation of Memory* is, perhaps, farther afield than some, but it too is welcome, given the burgeoning entrepreneurial industry of "cognitive rehabilitation." In the light of my own biases and reservations, I was favorably disposed to the former and suspicious of the latter before reading either.

So much for preconceived notions. Khan's volume is disappointing, while I was repeatedly impressed with Wilson's sophistication, knowledge, caution, and evident clinical sensitivity.

To write a carefully crafted, sufficiently detailed introductory text, one of "an educational series for residents and clinicians" that proposes to cover both fundamental and clinical aspects of memory dysfunction, is certainly a difficult task. Dr. Khan's book represents a superficial, unprocessed literature review rather than the product of intimate involvement with treating or studying amnestic or other memory-impaired patients. There are many specific problems with this work as well.

For example, although the literature of the past decade has grown rapidly, I found few references beyond 1982. Occasionally I encountered a 1983 or 1984 reference and once a 1985 reference, but these were the exceptions. Chapter 1, "Nature of Memory," has no discussion of important ideas regarding "effortful" and "automatic" aspects of memory or the very important recent research comparing declarative (information-related) versus procedural (skill-acquisition-related) memories. More striking is the absence of any recognition of the neurobiological studies of Mishkin and his colleagues. Similarly, chapter 2, "Memory Assessment," is composed of uncritical, brief descriptions of different test procedures without any apparent appreciation of their strengths and deficiencies.

How can a book such as this have a discussion of kuru and subacute sclerosing panencephalitis, which is rapidly disappearing, but no well-formulated consideration of the Wernicke-Korsakoff syndrome or transient global amnesia or herpes encephalitis? And why is the title of chapter 5 "Role of Neuropeptides in Memory" when the chapter includes the monoamines, noradrenaline, dopamine, serotonin, and acetylcholine?

Clearly, I was disappointed in Khan's book, and neither students nor clinicians should seek answers here. For questions about specific disorders, I would turn to Lishman's *Organic Psychiatry* (1). In addition, Squire's *Memory and Brain* (2) provides a thoughtful, current introduction to the psychology and neurobiology of memory.

Wilson's *Rehabilitation of Memory* is, within its own clearly defined limits, a very impressive book. This author knows her work, obviously having been immersed in both the clinical and scientific application of memory theory to the practice of cognitive rehabilitation.

Cognitive rehabilitation is currently a growth industry in the United States, especially for young patients with traumatic head injuries. Its rapid development reminds me of the recent experience with cardiac bypass surgery, where a field blossomed forth (soaking up many precious health dollars) before anyone could evaluate its proper place in the range of available therapies. Once effective research was conducted, we learned that the population suited for bypass operations was relatively limited. Similarly, we have no well-conducted research to indicate whether cognitive rehabilitation is better for healing than time alone or on whom we should focus our efforts and resources.

Wilson provides the necessary background for ultimately defining the utility of memory retraining. One finds brief, well-conceived discussions of contributions from neuropsychology, cognitive psychology, and behavioral psychology. Wilson shows no doctrinaire biases when drawing from all these fields to creatively develop programs for patients. I was pleased with her consideration of the utility of single case studies and repeatedly reassured by her insistence on careful experimental controls.

Despite an obvious sensitivity to research design, Wilson's is primarily a clinical book, full of carefully considered case examples. Moreover, the author does not make grandiose or farfetched claims but, rather, describes results modestly and considers realistically that the gains of some patients were evident when measured by clinical assessments but less apparent in their day-to-day functioning.

The utility of Wilson's book goes beyond the traumatically injured or the postencephalitic patient. Many of the training strategies and assessment paradigms would apply as well to demented patients participating in pharmacotherapeutic trials. Indeed, I wonder whether memory retraining is an essential and necessary experimental setting for studying the efficacy of future medications for Alzheimer's disease.

In sum, the focus of *Rehabilitation of Memory* may not appeal to as many psychiatrists as the focus of *Clinical Disorders of Memory*. However, the former is an outstanding work, easy to read, thoughtful, and, at times, inspiring. Although it does not answer the clinician's or the insurer's questions about the efficacy of cognitive rehabilitation, it provides both the clinical and experimental frameworks for addressing these issues.

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Sleep, Aging and Related Disorders, *edited by W. Ulmser, D. Kurtz, and W.B. Webb. Basel, Karger, 1987, 157 pp., $69.50.*

This volume contains the proceedings of an international symposium on sleep disorders held during the 13th World Congress of Neurology in 1985. It is an interesting if somewhat narrowly focused compendium of data and reviews from an active and productive field investigating both the healthy and the pathological effects of aging on the timing and structure of sleep.

The introductory chapter by W.B. Webb, one of the deans of North American sleep research, provides a scholarly review of what is known about changes in sleep associated with healthy aging. The increasing fragmentation of sleep and loss of depth of sleep with aging represent robust effects. A new wrinkle in this story is suggested by Webb's report that intraindividual sleep characteristics are quite stable in older individuals. I agree with Webb that we need more longitudinal sleep data in older, pathology-free subjects and, he might have added, in the old old. Webb's recommendation that further research be focused on the role of biological rhythms in late-life sleep structure and timing is cogent.

The chapters by Lugaresi et al., McGinty et al., and Sullivan et al. provide clinically useful, data-based reviews of sleep-related breathing disorders in aging. The epidemiologic significance of this area is probably vast, considering that sleep-disordered breathing occurs in 25% of the older population and could contribute to the higher risk of stroke, myocardial infarction, and death during sleep in the elderly.

Moreover, as the reviews of these authors point out, there is now ample evidence linking sleep apnea and/or hypopnea in the elderly to cognitive dysfunction, hypertension, insomnia, and daytime sleepiness. Possible mechanisms of the negative effects of sleep on breathing in late life include dissociated activity of intercostal and diaphragmatic muscles during REM sleep, failure of autonomic control of respiration, hypotonia of oropharyngeal muscles, and decreased sensitivity of respiratory centers to metabolic stimuli. The need for controlled trials of pharmacologic and nonpharmacologic treatments is considerable.

Alexander Borbely, a distinguished pharmacologist and sleep researcher at the University of Zurich, has written the most objective review I have seen of the effects of tryptophan on sleep. He concludes that it may induce drowsiness and reduce sleep latency (the time it takes to fall asleep) if given in adequate doses (generally more than 3 g) but that the effects appear to last for only a short time. Published data suggest no clear relation between tryptophan dose and response or relation between response and type of insomnia (particularly sleep continuity disturbance, which is more common than difficulty in sleep initiation in the elderly).

On this side of the Atlantic, Patricia Prinz's contributions to our understanding of sleep changes in abnormal aging are nicely reviewed in her chapter on Alzheimer's dementia. Prinz's group at the University of Washington have been particularly interested in how the advance of dementia affects REM sleep and associated changes in neuropsychological function and, conversely, how the preservation of REM sleep in healthy aging is associated with the integrity of information-processing capacity. More recently, this team has courageously undertaken the study of biological rhythms in dementia. Their preliminary conclusion is that dementia does not affect the body's mean 24-hour temperature, amplitude of day versus night differences in temperature, and the timing of peaks and troughs in circadian temperature rhythms.

Continuing the focus on neurological disease, the final chapter by Emser and colleagues presents data on sleep physiological alterations associated with Parkinson's disease and Huntington's disease. These data will interest those concerned with brain mechanisms of sleep. A particularly intriguing observation that will require further study is the possibility of greater sleep spindle density in patients with Huntington's disease and in first-degree relatives of such patients who are at risk for the disease. Will greater spindle density prove to be a marker for Huntington's disease, much as decreased REM sleep latency may be a marker for those at risk to develop major depression?

Apropos of depression, there is hardly a word about it in this book. Given the importance of depression in late life, its simultaneous occurrence with neurological disease, and the considerable data base on sleep, depression, and aging, I consider the absence of a systematic review of this area to be a major flaw. Similarly, in my opinion, inadequate attention is paid to the ontogeny of biological rhythms, to the epidemiology of late-life sleep disturbances, and to the interrelationship of sleep and neuropsychology. A disproportionate emphasis is accorded to sleep-related breathing disorders at the expense of these other topics. Thus, the overall value of this volume as a truly interdisciplinary undertaking in gerontology is less than it might otherwise have been.

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DIAGNOSIS AND TREATMENT

Doctors, Patients and Placebos, *by Howard Spiro. New Haven, Conn., Yale University Press, 1986, 261 pp., $27.50.*

This is a wise book and a scientific book, and few internists since William Osler are as much fun to quote as Howard Spiro. Scholars of medical anthropology may be disappointed with his cross-cultural discussion of the placebo, and students of holistic medicine and miraculous cures are sure to be. For Spiro has not written a book about relieving pain through illusion or curing disease through mind over matter. Indeed, Spiro cautions us that only a physician trained in science should be trusted with a placebo. Thus, he wrote to both Norman Cousins and his physician for a more objective account of Cousins' medical history. He received nothing from the doctor and only an inscribed copy of *Anatomy of an Illness* (1) from Cousins. Spiro makes his point without a sermon.

Healing comes not from the placebo as illusion, Spiro writes, but in the relationship that the placebo forms between the healer and the patient. Thus, with the wise use of placebos, the person is helped even if the disease goes unchanged. "Dis-ease" is relieved, pain is medicated, comfort is provided, and, most important, a relationship is forged. The use of placebo should convey to the patient an honest scientist striving to do good; thus, "Words must accompany therapy if illness is to be helped." But Spiro also warns that "the placebo does not create loyalty; the physician must give it; the placebo is powerless without the physician." The placebo is metaphor, and Spiro suggests that physicians need to regain confidence in the symbolic reality of medicine. "Ever since the Enlightenment," Spiro writes, "physicians as a group have come to see themselves as physicists, not as poets. One of the reasons why we overtreat and overstudy and cannot always talk with, or even listen to, our patients is that most of us are too busy looking at their organs and functions. The eye, as I will emphasize, rules the ear."

All medical students and all experienced general physicians who have not yet lost the ability to see fresh, broader, and clearer vistas in their profession will gain from this book. But psychiatrists who aspire to the "medical model" may benefit the most. In their headlong rush to make psychiatry ever more "scientific," these psychiatrists will do well to heed this wise professor of medicine. As a leading gastroenterologist he has witnessed the revolution that radiologic imaging has brought to accurate diagnosis in his specialty. But as he has seen his colleagues put more and more emphasis on the use of their eyes, he has watched them forget how to listen. He documents that the course of a patient's ulcer crater does not always parallel his or her discomfort. "The imaging revolution of the 1970's and 80's has pushed medicine into the silent art again," because a physician's eyes see the disease, but it requires a physician's ears to see the patient.

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New Brain Imaging Techniques and Psychopharmacology: British Association for Psychopharmacology Monograph 9, *edited by Michael R. Trimble. New York, Oxford University Press, 1986, 130 pp., $45.00.*

The use by psychiatric researchers of recently developed brain imaging techniques (computerized tomography, magnetic resonance imaging [MRI], positron emission tomography [PET], and brain electrical activity mapping) has allowed in vivo testing of long-held hypotheses regarding the involvement of cerebral biological involvement in mental illness. To date, most books dealing with these new techniques have examined only theoretical underpinnings or recent research findings. In general they have not cast a critical eye on methodological assumptions, inherent limitations, and optimal imaging strategies for patients in a psychiatric context. This volume manages to address many of these issues. Its major emphasis is on nuclear medicine techniques in brain imaging, especially PET. This is appropriate in a book with a primarily psychopharmacological bias.

There is a considerable amount of valuable insight and information packed into this slim book. The 10 chapters, which are predominantly above average in quality, range from broad critical discussions of an entire field (for example, PET scanning) to narrower presentations of findings and selected experiments conducted by the authors themselves. Five chapters deal with PET scanning and two with MRI. Other chapters discuss where these techniques might lead in the context of psychiatric research. The most valuable part of the book for me was the carefully considered and concisely written early chapters on the theoretical and experimental basis from which PET scanning evolved. These chapters examine the important practical issue of which experimental questions the technique is and is not capable of addressing, given inherent technological limitations.

This book contains contributions from many well-known investigators and will appeal to a broad audience. It should be of interest to general psychiatrists who want to review the wide range of studies currently carried out in neuropsychiatric illnesses such as epilepsy, stroke, dementia syndromes, and schizophrenia. Additionally, for reasons already stated, the volume will be of considerable interest to researchers specializing in brain imaging.

There are some qualifying observations. In addition to contributions from the productive hives of well-known researchers, the occasional chapter evidences breadth at the expense of depth. Also, although the date of publication is 1986, some of the "possibilities" to which it alludes are currently distinct and vigorous enterprises, having grown considerably since the chapters were written. It is perhaps inevitable in a fast-moving field that new knowledge and events will make published material outdated before it clears the presses.

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Handbook of Psychiatric Drug Therapy, *by Steven E. Hyman and George W. Arana. Boston, Little, Brown and Co., 1986, 173 pp., $15.00 (paper).*

Books on clinical psychopharmacology require a difficult balancing act. The authors have to present both the well-worn grooves and the cutting edge of the field, avoid the appearance of uncritical shills for every new drug or "new indication," and convince clinician readers that the subjects treated were not just test tubes, white mice, or preposterously winnowed research patients. So when the present text stakes its claim to being "a practical guide to the use of the various categories of modern psychiatric drugs . . . written primarily for the prescribing psychiatrist," the reader's eye might be well be sharpened by a bit of nonpathological jaundice.

We could initially judge this book by its cover, which tells us that it belongs to the Little, Brown Handbook series. This immediately evokes positive transference memories of previous handbooks from this publisher—the "Washington Manual" (still the rescuer of residents on many a late night) (1) and the excellent but lamentably still unrevised *Manual of Psychiatric Therapeutics* edited by Richard Shader (2). In fact, the present handbook is a descendant of the latter in its geographic, academic, and publishing lineage. Next we notice the book's superior design: highly pleasing typography, exceptionally clear figures, well-conceived tables, a gratifying scarcity of typographical errors, and a sturdy binding.

The book's contents confirm the promising first impression. Hyman and Arana first give an excellent three-page précis of their approach to drug therapy, which should be required reading for everyone with access to a prescription pad. Then they provide a series of chapters on the major classes of psychotropic medications, including not only the old standbys but also drugs such as anticonvulsants for psychiatric indications, β-blockers, and clonidine. For each drug group, the authors furnish a succinct but extremely informative account of the pharmacology, hypothesized mechanism of action, indications, therapeutic use (including use for special populations), drug interactions, and symptoms and management of side effects and toxicity. The section on carbamazepine, for instance, is the best practical overview I've seen anywhere. The text material is accessible through the general index as well as a special listing that cross-references specific disorders and clinical situations with their indicated drugs.

Throughout, the authors weave the available empirical data together with sensible reservations and recommendations about fads and ill-defined areas. Consider, as just two examples, their comments on very high neuroleptic doses ("often more reflective of physician frustration than therapeutic need") and on the dexamethasone suppression test (DST) ("drug therapy for depression should never be withheld because of a negative DST"). They consistently convey that they treat real-life patients while pursuing rigorous scientific knowledge.

Flaws in this book are hard to find. The authors are a bit more enthusiastic than the available data warrant regarding the efficacy of psychostimulants for "apathetic and withdrawn states in the medically ill and elderly," but this is a minor quibble. For the next edition—which the book will certainly deserve—a wish list might include more white space for the margins, perhaps a short section on disulfiram, and a bit thicker cover, because this book will be used. It delivers more value for its price than others costing three or four times as much; every psychiatric resident and practicing psychiatrist can and should own a copy. This book is highly recommended.

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Reprints of Book Form reviews are not available.

Letters to the Editor

Inadvertent Imipramine Challenge in Panic

SIR: Several lines of evidence suggest that panic disorder and major depression are closely linked. 1) Many patients with panic disorder have current and/or past major depression (1, 2). 2) Relatives of patients with both major depression and panic disorder may be more likely to have major depression, panic disorder, and generalized anxiety disorder than relatives of patients with major depression only (3). 3) Most polycyclic antidepressants and the monoamine oxidase inhibitors are effective in treating both panic disorder and major depression (4). In addition, increased platelet dihydroergocryptine binding and blunted growth hormone response to clonidine, which presumably reflect alterations in noradrenergic function, occur in both panic disorder and major depression (5). However, patients with these disorders appear to differ in regard to REM latency, response to sleep deprivation, and response to dexamethasone (5).

Clinically, we have noticed that some panic disorder patients may experience increasing panic attacks if they are started on too high a dose of imipramine. This has seemed so common that we have referred to it as the "inadvertent imipramine challenge test." Here we report a case in which a patient with major depression who denied any history of panic attacks experienced a full-blown panic attack after she had taken 50 mg/day of imipramine for 3 days.

Ms. A, a 35-year-old white married woman, said that over the preceding 8-12 months she had had increasing feelings of depression characterized by awakening two or three times a night, poor appetite, reduced energy, anhedonia, and guilt ruminations. She stated that these symptoms were increasing in intensity. She denied any previous history of major depression or panic attacks and any other major psychiatric problem. Her family history included Parkinson's disease in a maternal grandmother and Huntington's chorea in an unidentified paternal relative.

She was started on 50 mg/day of imipramine. On the fourth day, shortly after having arisen in the morning, she experienced the sudden onset of cold sweats, weakness, a feeling of faintness, dizziness, shakes, chest tightness, palpitations, shortness of breath, depersonalization, and fearfulness. She recognized the possibility that these symptoms might have been drug induced and stopped taking the medication. She discussed the symptoms with her psychiatrist, but refused to try another class of antidepressants and chose to continue the imipramine at a lower dose. At a dose of 25 mg/day, she reported brief episodes of numbness in her arm at one time and hot flashes at another, but she wished to continue taking imipramine.

For reasons yet to be elucidated, the antipanic activity of imipramine appears to be preceded by a period of time in which panic attacks may be triggered in the patient. Perhaps imipramine first stimulates locus ceruleus activity and then reduces its firing. This case is remarkable because the patient denied a history of panic attacks. Although she may have had them and not recalled them, her experience highlights the possibility that imipramine triggers these attacks in people already known to have panic attacks. In addition, Ms. A's response raises the continuing question about the relationship between panic disorder and depression.

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Psychogenic Catatonia Treated With Lorazepam

SIR: We read with great interest the report by Sultana A. Salam, M.D., and associates on the treatment of psychogenic catatonia with lorazepam (1). We would like to contribute the following case report.

Mr. A, a 25-year-old man with a 5-year history of schizophrenia, undifferentiated type, was admitted to the hospital. On admission he was described as mute, with marked psychomotor retardation. The results of a physical examination and laboratory tests were normal, as were an EEG and a computerized tomography scan with contrast. He was being treated with oral doses of trifluoperazine, 10 mg q.i.d., and benztropine, 2 mg b.i.d. A diagnosis of schizophrenia, catatonic subtype, was made.

Over the next 2½ years the patient's condition did not improve. He uttered only occasional monosyllables to the nursing staff and finally became totally mute. He had markedly decreased psychomotor activity and exhibited waxy flexibility. He required nursing assistance to dress, eat, and bathe and was also frequently incontinent of urine.

Repeated neurological examinations and laboratory tests failed to demonstrate any organic pathology. Numerous treatments were tried during the course of the hospitalization: 1) trifluoperazine, 10 mg q.i.d., for 6 months;

2) perphenazine, 8 mg b.i.d., for 6 months; 3) two courses of bilateral ECT (five treatments initially, followed by six treatments 7 months later); 4) trazodone, 50 mg t.i.d., for 6 weeks; 5) desipramine, 25 mg t.i.d., for 8 weeks; 6) clomipramine, 25 mg t.i.d., for 6 weeks (both the desipramine and the clomipramine were at therapeutic serum levels despite the low doses); and 7) combined carbamazepine, 200 mg t.i.d., and lithium carbonate, 450 mg b.i.d., for 4 weeks (both with therapeutic serum levels). These treatments had little or no effect.

Finally, Mr. A received lorazepam, 2 mg i.m. Initially there was no response, but 4 hours after the injection he suddenly started talking. He was alert and oriented and exhibited normal psychomotor activity. He denied symptoms of depression and smiled frequently during the interview. He had somatic complaints but denied abnormalities of thought content or perception. He could not explain his former mutism and psychomotor retardation. He exhibited thought blocking and loosening of associations and had no insight regarding his illness.

This effect lasted approximately 12 hours. His medications were changed to oral doses of pimozide, 12 mg h.s.; benztropine, 2 mg b.i.d.; and diazepam, 10 mg h.s. (Diazepam was chosen for its longer half-life.) Mr. A's psychomotor activity increased but never became completely normal. He no longer exhibited waxy flexibility. He remained mute with the staff but started to speak to his mother and his wife. Soon after, he was able to be discharged to the care of his family.

The mechanism of action of parenteral lorazepam in relieving catatonia is unclear (2, 3). However, this case shows that it may have an important role in relieving longstanding schizophrenic catatonia that has proven resistant to other forms of therapy. It also demonstrates the previously reported benefit of adding diazepam to the medication regimen (4).

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Depressive Illness With Delusions of AIDS

SIR: With the increase in the incidence of acquired immune deficiency syndrome (AIDS) in recent years, there has been a spate of articles in medical journals about the physical and psychiatric aspects of AIDS. Miller et al. (1) discussed a case of depression and a case of anxiety in homosexual men. Many other articles (e.g., 2, 3) have discussed psychiatric morbidity in high-risk groups of patients. I would like to report the following unusual case.

Ms. A, a 62-year-old Caucasian housewife, was first seen at home at the request of her family doctor. Over the preceding few weeks she had complained of having AIDS and was feeling depressed and guilty about this. She boiled her eating utensils, washed her clothes separately, and had taken to her bed to avoid contact with other members of her family. She had lost an indeterminate amount of body weight as a result of her reduced appetite.

There was no antecedent history of psychiatric or major physical illnesses. Ms. A's sister and two sons suffered from schizophrenic illness, and her daughter had recently been admitted to a hospital because of a brief psychotic illness. There was no evidence of personality problems or drug or alcohol abuse.

On admission to the hospital, Ms. A was found to be depressed, with psychomotor retardation and delusions of having AIDS and being infectious. She had no other delusions and was cognitively unimpaired.

Soon after admission, she made a low-visibility suicide attempt by cutting both her wrists and needed surgical intervention. She later stated that she did this to prevent the spread of the disease. She refused food and medication but was treated with eight ECTs after the appropriate procedures under the 1983 Mental Health Act had been followed. She made a remarkable recovery and remained well at 6-month follow-ups while on a regimen of antidepressant medication.

It is well recognized that the content of delusions is subject to pathoplastic sociocultural influences. This case is an example of this. Since AIDS has been widely discussed in the media and is said to have high fatality, it is understandable that collective anxiety in the general population is high. However, it is important, especially for mental health professionals, to be aware that the presenting complaint of "fear of AIDS" may be just one aspect of much more serious underlying psychopathology. In this patient's case, it was not very difficult to suspect and treat the psychotic depression, but it might be more easily overlooked in younger, high-risk patients.

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An Attempt to Commit Suicide by Contracting AIDS

SIR: I read with great interest the letter by Richard J. Frances, M.D., and associates (1) on contracting acquired immune deficiency syndrome (AIDS) as a means of committing suicide and the article by Daniel K. Flavin, M.D., and associates (2) in which they reported on four alcoholic homosexual men who deliberately sought to be infected by AIDS with the purpose of committing suicide. I would like to report briefly on a similar suicide attempt by a woman.

Ms. A, a 23-year-old single professional woman, described to me her attempt to commit suicide, after she was deserted by her lover, by deliberate infection with AIDS through intimate contact with a carrier of the AIDS virus. The patient was an only child; her father had never been close to her and her mother was overprotective. From childhood on, her self-confidence had been low and she had had the concomitant feelings of insecurity and uncertainty. She had no history of alcohol intake or homosexual practices.

Ms. A had had suicidal thoughts for several years but found it difficult to kill herself. After the desertion by her lover, when she decided to become infected with AIDS, she tried to have sexual relations with an AIDS-virus carrier, but he was reluctant at first to comply with her request, so she had to be seductive in order to be successful with him. This was her first attempt at suicide, and there was no family history of attempted suicide.

On initial evaluation, 4 months after her suicide attempt, Ms. A complained of intense anxiety, anorexia, insomnia, and inability to work, despite the fact that the results of the special test for AIDS antibodies were negative. She appeared depressed and had feelings of guilt and shame about the attempt. She fulfilled the *DSM-III* diagnostic criteria for adjustment disorder with mixed emotional features. My therapeutic goal was to reinforce her ego defenses, strengthen her self-esteem, prevent her social withdrawal, overcome the disturbed daughter-parent relationship, and return the patient to her usual activities.

This case is different from the four previously reported (1, 2) in that it concerns a woman, and she was not alcoholic or homosexual; it is similar in that a deliberate attempt to contract AIDS was chosen as the means of committing suicide. I agree with Dr. Frances and associates (1) and Dr. Flavin and associates (2) that these patients projected murderous wishes in seeking out another as an "executioner" (3). Moreover, my patient tried to seduce her executioner in a fashion reminiscent of Loewenstein's "seduction of the aggressor" (4).

These samples of five patients, although limited in number, suggest that physicians and other interested persons should be aware of this potential problem with suicidal patients.

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Sex Differences in Panic Disorder

SIR: The preponderance of women among persons with panic disorder is a consistent epidemiological finding (1). The explanations for this are mostly speculative and range from socioeconomic to psychological. The significance of this difference, however, could be etiologically relevant to the disorder.

Having conducted hundreds of lactate infusions in patients with panic disorder, we have reported changes in a great number of parameters before, during, and after the infusions (2) but have found few significant sex differences. Recently identified ventilatory and acid-base changes during lactate infusions (3), however, have brought into focus a relatively neglected area of research: the respiratory physiology of panic. In order to evaluate the exact acid-base status of panic patients, we started collecting arterial blood samples during lactate infusions. The procedure, described in detail elsewhere (2), consists of a 30-minute saline infusion (baseline) followed by a 20-minute infusion of 0.5 M sodium lactate.

Analysis of the baseline arterial blood gas samples revealed that male panic disorder patients who subsequently panicked when given lactate (N=5) were in a state of mild, chronic, compensated, respiratory alkalosis (normal pH, low arterial P_{CO_2} and low H_{CO_3} level) and developed superimposed, acute respiratory alkalosis (significant drop in arterial P_{CO_2}). In fact, an arterial P_{CO_2} of 40 torr or higher at the time of the switch to lactate virtually precluded lactate panic in male patients. Male panic patients who did not panic when given lactate (N=8) maintained normal pH, arterial P_{CO_2} and H_{CO_3} values and did not hyperventilate during the baseline period.

By contrast, there were no significant acid-base changes for female patients during the baseline period and no significant baseline acid-base differences between female panic patients who panicked when they received lactate (N=10) and those who did not (N=11). Female patients as a group maintained blood gas values consistent with mild, chronic, compensated respiratory alkalosis. At baseline, female patients who panicked after lactate were indistinguishable from female patients who did not panic. Acute hyperventilation thus seems necessary for lactate panic to occur in men but not in women. A tendency to hyperventilate at baseline may be a characteristic feature of lactate-sensitive male, but not female, panic patients.

We do not have data about the time of the procedure in the female patients' menstrual cycles. This factor could significantly alter these findings. A larger sample size is clearly needed to substantiate these preliminary results. However, if they are replicated, differences in respiratory physiology could indicate a distinct characteristic of lactate-sensitive male panic patients that differentiates them from female patients with panic disorder.

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Opening the Mouth to Abolish Auditory Hallucinations

SIR: Peter A. Bick, M.D., and Marcel Kinsbourne, M.D. (1) recently reported that the maneuver of opening the mouth widely had been useful in abolishing auditory hallucinations in 14 of 18 schizophrenic patients tested under experimental conditions. The authors found this to be consistent with the hypothesis that auditory hallucinations result from the misinterpretation of the individual's own subvocalizations (2), since opening the mouth has been shown to prevent subvocalization in normal subjects (3). Unfortunately, the patients of Drs. Bick and Kinsbourne showed no interest in using the maneuver to control their hallucinations on their own. We recently treated a patient who was able to use this technique in a therapeutic manner.

Mr. A, a 57-year-old married maintenance worker, was first hospitalized at age 10 for visions and affective changes. At age 20 he began to hear voices commenting on his behavior, and subsequently he developed catatonia. Diagnosed as schizophrenic, he was hospitalized for 8 years in a state facility, where he received trials of insulin therapy, ECT, and neuroleptics. He was then maintained as an outpatient on neuroleptics and tricyclics for over 25 years, although he continued to have auditory hallucinations and religious preoccupations and to do ritualistic counting and tapping.

On admission to the hospital, Mr. A manifested a depressive syndrome associated with obsessions and compulsions. He also reported a longstanding symptom of hearing voices that kept up a running commentary on his behavior, often telling him to perform certain tasks. After he gave informed consent, his previous neuroleptic/tricyclic regimen was tapered and then discontinued and he was maintained, double-blind, on placebo for 1 month. During this time the intrusiveness and frequency of his hallucinations increased markedly, and he developed great difficulty in washing and dressing because of the commenting and commanding voices.

To test the efficacy of the mouth-opening technique, Mr. A was first instructed to raise his right hand and concentrate on its image, after being told that this procedure had been shown to decrease voices. He reported no change in his auditory hallucinations. He was then instructed in the mouth-opening technique, which he found decreased the hallucinations "almost 100%," to his great relief. He subsequently used the technique successfully while showering and dressing and later used it to control breakthrough hallucinations while he was on active medication. Follow-up of this patient was limited to the duration of his approximate 12-week hospitalization; however, he used this technique successfully and of his own volition until the time of discharge.

As noted elsewhere (4), some patients are able to exert self-control of their psychotic symptoms through self-instruction, increased activity, or decreased activity. The mouth-opening maneuver may offer rather specific benefits for the self-control of auditory hallucinations. Systematic study would be useful to clarify which patients are most capable of using this technique.

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Nausea From Taking Both Lithium and Trihexyphenidyl

SIR: An anticholinergic drug, trihexyphenidyl, induced troublesome nausea in three male patients who were concurrently taking lithium carbonate as part of a study of lithium's side effects. The patients were 24, 29, and 62 years of age and were taking 2400, 1500, and 1200 mg/day of lithium carbonate, respectively. The three patients had some common clinical features: 1) before they took trihexyphenidyl, there was complete therapeutic response to lithium carbonate alone for acute mania, 2) annoying nausea began within 2 hours of the first dose of trihexyphenidyl, 3) nausea continued until the trihexyphenidyl was stopped, at which time it disappeared completely, and 4) the administration of lithium, without dose reduction, continued throughout the appearance and disappearance of nausea. Slow-release lithium preparations were not used. Two patients vomited. After the nausea disappeared, the 29-year-old was again given trihexyphenidyl, and the nausea returned.

Nausea developed rapidly and uniformly after just 5 mg of trihexyphenidyl were given, indicating that the combination of lithium and an anticholinergic agent might affect some patients adversely at lower doses. If the nausea results from physical pathology (e.g., gastric irritation), there might be adverse health consequences in suppressing nausea and allowing the physical pathology to continue. Because neuroleptics powerfully block nausea, such a situation might occur clinically when neuroleptics and anticholinergics are combined with lithium in treating acute mania.

By itself, trihexyphenidyl is not known to induce nausea. The nausea we observed might have been generated by exposure of the stomach wall to lithium carbonate; its high pH value of 13 tends to irritate gastric mucosa (1). Anticholinergic agents reduce acid, mucin, and total secretion in the stomach, weakening mucosal insulation from stomach contents. Anticholinergics also decrease gastric and intestinal motor activity (1), slowing stomach emptying. In these circumstances, use of aluminum hydroxide gels might prevent stomach irritation and nausea by lining the mucosa and lowering the stomach pH value. Using lithium citrate (pH=4.7) (2) instead of lithium carbonate might also be useful.

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Criteria for Alcohol Dependence in *DSM-III-R*

SIR: Among the criteria for alcohol dependence (within the framework of psychoactive substance dependence), *DSM-III-R* describes such biomedical criteria as withdrawal symptoms and increased tolerance to the substance. However, in contrast to opiate dependence, increasing tolerance plays a small role in maintaining alcohol dependence. Moreover, as I have indicated elsewhere (1, 2), in the later stages of alcoholism, tolerance is frequently reversed (a fact that both *DSM-III* and *DSM-III-R* fail to mention). *DSM-III-R* also suggests a number of behavioral and social criteria: 1) the substance is often taken in larger and larger amounts, 2) the person has a persistent desire to or has made one or more unsuccessful efforts to cut down or control use of the substance, 3) a great deal of time is spent in activities necessary to obtain the substance or in recovering from its effects, 4) there are frequent intoxication or withdrawal symptoms when the person is expected to fulfill major obligations, 5) important social, occupational, or recreational activities are given up or reduced because of substance use, and 6) the person continues to use the substance despite having persistent social, psychological, or physical problems.

These criteria, however, are in fact the manifestations of physical or psychological dependence. Inclusion of such arbitrary selected secondary manifestations in the category of basic criteria is of questionable value. One can add to those "criteria" a number of others, such as solitary drinking, avoidance of family and friends, feelings of guilt, fears, and geographical escape.

DSM-III-R also indicates that one "species" of alcoholism, so-called gamma alcoholism (characterized by loss of control), is common in the United States, whereas another species of alcoholism, associated with inability to abstain, is common in France. Then, in a somewhat confusing fashion, the manual contends that "although these two pure types of alcoholism do exist, they do not conform to the pattern of drinking seen in most people with Alcohol Abuse or Dependence in the United States." Does this statement mean that most American alcoholics meet criteria for a specific species of alcoholism? (There is not enough epidemiological evidence to support such a suggestion.) Or does it simply mean that the criteria for alcohol abuse differ from those for alcohol dependence? It is not necessary to reemphasize this obvious difference in such a vague manner.

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Treatment of Borderline Patients

SIR: The study of the effects of long-term hospitalization on borderline patients by Lyle Tucker, Ph.D., and associates (1) was presented by them as if the most important variable involved were length of treatment, leaving the reader to take for granted as both appropriate and legitimate a highly controversial psychotherapeutic approach to the treatment of these patients. Based on the psychoanalytic theories of Otto Kernberg, this approach, in the authors' words, centers on "the patient's transformation of intrapsychic impairment into interpersonal discord [which] is not only allowed but encouraged."

However, other authors—notably Kohut (2) and Brandchaft and Stolorow (3)—have suggested that this approach, which fosters the enactment of negative transference reactions, is not only contraindicated with patients suffering from severe narcissistic vulnerability but indeed may exacerbate borderline symptoms. The prolonged hospitalization of these patients may not result from the initial severity of their pathology but be the outcome of treatment itself. The authors offered many suggestions about why they did not want to adopt what they themselves said would be the most straightforward conclusion from their data, namely, that therapeutic outcome is unrelated to length of hospitalization. I submit that by virtue of their particular theoretical orientation, Dr. Tucker and associates were unable to raise questions about the whole basis of what may have been a highly problematic treatment program.

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Interaction of Danazol and Carbamazepine

SIR: Dorothy O. Lewis, M.D., and colleagues have suggested a relationship between bipolar mood disorders and endometriosis (1). The clinician who treats a patient with this combination of disorders should be aware of the potential for a significant drug interaction. Danazol is a synthetic androgen used in the treatment of endometriosis. It has also been used for premenstrual syndrome (2) and rapid-cycling manic-depressive illness (3). There has recently been a tremendous increase in the use of carbamazepine in attempts to treat mood disorders, particularly rapid-cycling manic-depressive illness. Two recent reports (4, 5) have shown a significant decrease in carbamazepine clearance with the addition of danazol.

The earlier report (4) suggested that carbamazepine steady-state plasma concentrations may rise by 50%–100%—to 20 μg/ml or more—with an increase in clinical efficacy but no increase in carbamazepine-related adverse effects. It was suggested that this may be because concentrations of carbamazepine epoxide and other active metabolites

are reduced. More recently, Zielinski et al. (5) reported on a series of six women who had a 91.4% mean increase in carbamazepine concentration (from 7.55 μg/ml to 14.45 μg/ml) after danazol was added to their regimens. Five of these six patients had clinical signs of carbamazepine toxicity consistent with elevated plasma concentrations. Thus, additional studies are needed to clarify the clinical significance of this drug interaction.

Clinicians treating the population of patients described by Dr. Lewis and associates should be aware of this important drug interaction. It is not yet found in many of the available handbooks on drug interactions.

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Dosing Practices for High- and Low-Potency Neuroleptics

SIR: Several articles published in the *Journal* have emphasized physicians' dissimilar practices in prescribing doses of high- and low-potency neuroleptics. In 1984 Baldessarini et al. (1) found a 3.54:1 ratio between doses of high-potency and doses of low-potency neuroleptics prescribed for 110 Boston-area patients (mean±SD chlorpromazine equivalents=1184±125 mg for high-potency drugs versus 334±33 mg for low-potency drugs) and a 2.11:1 ratio in a sample of 16,000 Veterans Administration patients (1043 mg versus 494 mg; SDs not available). In a 1987 article, Zito et al. (2) reported a ratio of 2.7:1 (1137 mg versus 419 mg; SDs not available) for 136 patients. Both surveys were cross-sectional, but the latter restricted the diagnosis to schizophrenia.

We reviewed medication records of schizophrenic patients in a 900-bed psychiatric hospital to find patients who had been changed by prescriber preference from an oral neuroleptic of one potency type to another; this, in effect, created a retrospective cross-over design. Over the last year we found 35 such patients, 25 male (mean±SD age=33.8±7.1 years) and 10 female (43.9±14.2 years). Average doses were determined for the last 14 days a patient had received a neuroleptic before the change and then for the next 14 days when the patient was taking a neuroleptic of a different potency. Doses were converted to chlorpromazine equivalents by using the same potency ratios as were used in the previous studies (3). A ratio of 1.93:1 was calculated from a mean±SD daily dose of 1137.6±742 chlorpromazine equivalents for high-potency neuroleptics and 586.7±428 for low-potency neuroleptics. When intermediate-potency neuroleptics were included, as in Baldessarini et al.'s study (1), the ratio dropped to 1.66:1, with 1162.9±736 chlorpromazine equivalents for high-potency neuroleptics and 699.8±541 for drugs of low to intermediate potency.

Our findings confirm that clinicians use higher chlorpromazine equivalents in prescriptions for high-potency neuroleptics than for low-potency neuroleptics, but the ratio between the doses of high-potency and low-potency drugs was less dissimilar in our survey than in previous reports. Perhaps clinicians use these agents more comparably, on the basis of chlorpromazine equivalents, when they change the medications of schizophrenic patients to drugs with different potencies than they do in other clinical situations. The cross-sectional data obtained in earlier studies may reflect the prescriber's choice of neuroleptic, which is based on many factors, including diagnosis and severity of illness, history of previous response, age, sex, predisposition to certain side effects, and presence of other medical illness. Our study design may have minimized the influence of some of these many factors. In our sample, doses of high-potency neuroleptics were similar to those in the previous studies cited, but low-potency drugs were used in larger doses.

The use of chlorpromazine equivalents came into clinical practice shortly after the introduction of the various neuroleptic drugs. The validity of this practice has been supported by clinical observation and D_2-receptor-binding affinities (4). However, doses of high-potency agents were rapidly pushed upward in clinical practice to maximize clinical response. This was not possible with low-potency agents because of unwanted dose-related side effects. The more recent literature, which has included investigations of the relationship between plasma level and response, suggests that schizophrenic patients achieve adequate response with more conservative doses of high-potency drugs than one commonly encounters in clinical practice. As the impact of these studies becomes translated into clinical practice, it is possible that future surveys of prescribing practices will find a closer agreement between doses of high- and low-potency neuroleptics.

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Analytically Oriented Therapy of Homosexual Men

SIR: In a letter to the Editor (1), Harvey R. Greenberg, M.D., presented the history of a homosexual man who had originally renounced his homosexuality in a fundamentalist religious conversion, only to resume homosexual activity several months after his marriage. A psychiatrist is more likely to hear such a history from men who have been previously treated by psychoanalysts or analytically oriented

therapists than from those who have participated in a religious conversion (2).

Psychoanalysts still generally believe that heterosexuality is the only normal developmental end point, that homosexuality is caused by severe developmental disturbances, and that it is in the best interest of their patients to become heterosexual. While claims of success in converting highly motivated patients from homosexual to heterosexual behavior for certain periods of time vary from 20% to 50% (3, p. 277), Kinsey and his co-workers were surprised that they could not find one man whose sexual orientation, measured by a sustained change in sexual fantasy, had been changed by therapy (4, p. 252).

Some therapists directly encourage or exhort homosexual patients to give up their sexuality (5, 6). Most "neutral" therapists indirectly encourage this change by subtly reinforcing attempts at heterosexuality or by making homosexuality appear less desirable than heterosexuality. Both groups of therapists exploit the transference for the desired therapeutic gain. A therapist who is unaccepting of his or her patient as a homosexual man, who cannot demonstrate the same positive regard for the homosexual patient as for the heterosexual patient, is bound to reinforce damaging self-deprecatory or paranoid attitudes that may interfere with the patient's capacity to achieve and maintain fulfilling relationships (2).

The 1973 decision of APA to eliminate homosexuality per se as a mental disorder from *DSM-III* and the recent decision to remove ego dystonic homosexuality from *DSM-III-R* are largely ignored by psychoanalysts. I feel that psychoanalysis and dynamic, insight-oriented therapies influenced by psychoanalysis can be helpful to homosexual men in the ways in which they are helpful to heterosexuals and for the same spectrum of problems and disorders. Unfortunately, the moral value atmosphere of most analytically oriented therapies has made it impossible to measure their true potential for homosexual men.

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Psychodynamic and Behavioral Case Formulation

SIR: We read with great interest the article by Samuel Perry, M.D., and associates on the psychodynamic case formulation (1). The authors pointed out the lack of appropriate attention to case formulation in the psychodynamic literature and offered a set of guidelines for psychodynamic case formulations. Given the absence in the literature of such criteria, the authors should be commended.

It is interesting that one of the major criticisms of behavior therapy has been the lack of attention to case formulation. In particular, many psychodynamic therapists have attacked behavior therapists for holding superficial views of their patients. As practicing behavior therapists ourselves, we have also made that criticism of many practicing behavior therapists (2). While the problem of inattention to the case formulation apparently pervades the literature of both the psychodynamic and the behavioral therapies, it should be noted that behavioral definitions for case formulation were proposed in a structured format a decade ago (3). The criteria proposed for a behavioral case formulation are similar in some respects to those proposed by Dr. Perry and associates for a psychodynamic case formulation (although significant differences are evident). The behavioral case formulation includes an explanatory hypothesis that 1) relates all the presenting problems of the patient to one another, 2) explains why these difficulties developed, and 3) provides predictions of the patient's behavior in any given situation (i.e., resistance, therapist's style, etc.). Since the original proposal of a priori criteria for behavioral case formulation were published, numerous papers and books have appeared on the subject in the behavior therapy literature (4).

Regardless of theoretical orientation, the case formulation not only is integral to quality clinical work but holds significant potential for the advancement of scientific knowledge about psychopathology. Obviously, it is rather difficult to treat a problem that one does not understand. From a scientific point of view, we have yet to understand the majority of abnormalities that we encounter clinically. When clinicians develop good case formulations of poorly understood disorders, they are generating initial hypotheses that researchers can subsequently evaluate in scientific investigations. Accordingly, by developing good case formulations, a practicing clinician can not only increase his or her effectiveness but also contribute to the field at large. Be it by Freud or be it by Wolpe, the importance of case formulation was demonstrated long ago.

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Differences Among Patients With Posttraumatic Stress Disorder

SIR: In the article "A Laboratory Procedure for the Induction of Flashbacks" (1), John M. Rainey, Jr., M.D., Ph.D., and associates offered a description of "naturally occurring" flashbacks. Such flashbacks are reported by patients experiencing posttraumatic stress disorder (PTSD). However, the authors' description did not mention group differences. This

omission prevents a full appreciation of one of the observations in the article.

In civilian patients with acute PTSD, illusions and hallucinations have been reported (2). Such events are discrete and brief (3, 4), and there is little loss of identity.

The clinical picture in Vietnam veterans experiencing PTSD—the subject group used in the study by Dr. Rainey and associates—is quite different. These patients report a much more global experience, not reported by patients with acute PTSD, in which they feel as if they are back in the trauma scene (5). Such experiences can last for minutes to hours and include revisualizations, hallucinations involving other senses, illusions, and a concurrent loss of identity.

Since there are so many variables that differentiate acute PTSD in civilians from chronic PTSD in Vietnam veterans (the nature of the stressor, chronicity, substance abuse, etc.), reconciling these two different clinical pictures has been difficult.

Dr. Rainey and colleagues briefly mentioned, without elaboration, that patients who were experiencing revisualizations said that "having to concentrate on answering questions . . . kept them from dissociating completely." One can then hypothesize that reexperiencing events occurs on a continuum, with single revisualizations, such as those seen in acute PTSD, on one end and global dissociative behaviors at the other end of the continuum.

Future work with PTSD patients that uses the technique outlined by Dr. Rainey and associates or other anxiety-inducing stimuli (3) could more closely examine the reasons this progression occurs in one group and not another. Since such work provides a path to understanding other "hysterical" phenomena (e.g., hallucinations occurring during mourning, religious visions) I feel it would be quite worthwhile.

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ALLAN BURSTEIN, M.D.
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Mental Illness and Creativity

SIR: I greatly admired the article by Nancy C. Andreasen, M.D, Ph.D., on creativity and mental illness (1). Unfortunately, although she cited the limitations of the study in a necessarily brief manner, there is a risk that the casual reader may jump to the conclusion that it proves what some have suspected all along, namely, that creative people are indeed mad.

This study, in spite of the assessment of familial artistic accomplishments, seems to relate more to the occupation of writing than to creativity as such. A talent for words does not necessarily connote creativity. Moreover, those familiar with writers' lives will not be surprised by a high prevalence of depression, loneliness, financial insecurity, need for self-imposed structure, and regular expression of complex inner feelings. Good writing involves passion. When a story, poem, or book is finished, the experience is not unlike childbirth. However, becoming a parent is unlikely to trigger the rejection, hurts, disappointments, and indifference most writers encounter. "Author" seems to be one more occupation to be added to the list of those already characterized by a high rate of affective disorder and suicide (such as "physician") (2). Yet physicians are seldom characterized as notably creative.

The sparse literature on creativity and mental health actually suggests a positive, not negative, correlation between the two. Kubie (3) defined the creative act as the uncovering of new facts or new relationships among new and old data, requiring an active, successful collaboration between a well-organized, flexible ego and a preconscious unencumbered by denial and repression. Schubert (4), using Guilford's standardized tests of creative abilities and the MMPI, reported a significant relationship between creativity and successful emotional adjustment. In his study, subjects with high creativity scores showed significantly low scores on the MMPI for various forms of psychopathology and aberrant behavior.

Then, too, what is the real nature of affective disorders? It does not seem to me that being depressed is, in itself, necessarily unhealthy. Rather, I believe illness exists when a person cannot become appropriately depressed under conditions that warrant depression and/or cannot recover spontaneously from a depressed state within a reasonable amount of time (5). The experience of depression can even be positioned within the context of creativity itself, with episodes of depression constituting necessary preludes to new insights, fresh syntheses, and higher levels of adaptation (6).

Perhaps the writers Dr. Andreasen studied were more vulnerable to depression not because they were creative but because, like many physicians, they were more sensitive to the human condition than the control subjects, who were engaged in running hospitals and trying cases in courtrooms. These writers had consulted therapists in the past. Could this not indicate insight?

This is an invaluable study. I hope it stimulates profitable debate and innovative research on an extremely important but somewhat neglected topic.

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FREDERIC FLACH, M.D.
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Dr. Andreasen Replies

SIR: Dr. Flach's letter makes a number of important points, and it is useful to clarify some of the issues that he raises.

First, my article indicated an association between creativity and mental illness, but it did not make strong directional inferences. It predicted neither that creativity leads to mental illness nor that mental illness leads to creativity. I myself suspect that creative people have a characteristic underlying cognitive style that predisposes them to be both creative and vulnerable to fluctuations in mood. This cognitive style is characterized by curiosity and adventuresomeness, a refusal or inability to see the world through the eyes of convention and tradition, sensitivity and intuitiveness that permit imagining and experiencing a wide range of feelings and ideas, intellectual flexibility that is tied to a recognition of the transiency of life, and a willingness to take risks. This cognitive style is likely to generate more positive and negative life events, more subjective experiences of both happiness and sadness, and a fresh and innovative approach to almost any task that is undertaken.

On the basis of my experience in interviewing the writers, this cognitive style appears to run in families and to produce a combination of both creativity and affective illness in those families. Particularly striking is the fact that the other creative individuals in the families of these writers were not necessarily themselves writers. To me, that suggests a basic underlying cognitive style. If it happens to be coupled with a good Wernicke's area, then the person may become a writer. If it is coupled with a good motor cortex and extrapyramidal system, the person may become a dancer.

I certainly agree with Dr. Flach that creativity carries with it many benefits. In many respects, most of the writers whom I interviewed could be called well-adjusted. They were usually disciplined, determined, and persistent. They were also warm, sensitive, charming, and very interesting. I did, in fact, give all of them the MMPI, but I have never described these data because no consistent pattern could be observed in the profiles. I can say unequivocally that the writers did not have consistently low scores on MMPI indices of psychopathology, and I can say that they definitely did have episodes of affective illness as well. The conclusion that there is an association between creativity and affective illness in writers seems inescapable. Yes, most of them did seek treatment, but if we were to conclude that all our patients who seek treatment have insight and therefore are especially healthy, we would have to conclude that psychiatrists do nothing but treat healthy people.

These writers had an illness, albeit an intermittent one. If a careless reader assumes they were therefore "mad" or "crazy," that is indeed unfortunate. We must change such misperceptions through public education, but we should not change them by ignoring or misrepresenting facts. Ultimately, the association between affective illness and creativity is a comforting fact to patients with mental illness, since it implies that one can have such an illness and still make major contributions to society.

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Training in ECT

SIR: In an editorial in the *Journal* (1), Max Fink, M.D., raised the sensitive issue of psychiatric training in ECT in the United States. ECT, while it remains an extremely important treatment for serious psychiatric conditions, has been relegated to the lower levels of priority, if not totally ignored, in a number of training programs. Residents in some programs have completed training without any direct observation of ECT, while, in contrast, the clinical and basic sciences of ECT have been advancing. It is therefore encouraging to know that the matter of improved ECT training is being reviewed by components of APA, the American Board of Psychiatry and Neurology, and the International Psychiatric Association for the Advancement of Electrotherapy.

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Prescribing Lithium for Pregnant Women

SIR: A case report by Eduard M. van Gent, M.D., and Guido Nabarro, M.D. (1) described a woman with bipolar disorder who had been taking lithium and whose medication was changed to a low dose of haloperidol because of her wish to become pregnant; she continued to take haloperidol for the duration of her pregnancy. The authors noted that haloperidol and other high-potency neuroleptics are considered to have a low teratogenic risk and have been associated with few neonatal complications. They did not, however, fully consider the potential complexity of the clinical situation or the variety of options available to the physician. For example, although an increased number of cardiovascular malformations has been reported in infants exposed to lithium during the *first* trimester (2), its use in pregnancy, particularly *after* 12 weeks' gestation, is not absolutely contraindicated as the authors implied.

When treating a pregnant woman who has a psychiatric disorder, the physician must carefully weigh the risks of drug exposure against those of the untreated disorder. The risks, including the increased impulsivity associated with mania, have been well described, and the attendant risk to the fetus from an acutely manic mother is obvious. A pregnant patient taking lithium carbonate whose history includes only one circumscribed episode of mania or few past episodes is a good candidate for lithium discontinuation and close follow-up, as opposed to exposure to neuroleptic therapy with its potential risks. In addition to the low risk of tardive dyskinesia and the uncertain potential teratogenic or long-term neurobehavioral effects resulting from in utero exposure to antipsychotic agents, extrapyramidal symptoms lasting up to 6 months have been described in neonates exposed to these agents. For bipolar patients with a demonstrated need for prophylaxis against recurrent manic episodes, the putative antimanic agents carbamazepine and clonazepam may be preferred, since they apparently have a low teratogenic potential (3, 4).

Thus, the therapeutic algorithm varies with the clinical history of the patient and the relative need for antimanic prophylaxis. If recognition of pregnancy occurs in the second

or third trimester, continuation of lithium therapy in some cases may be a more reasonable course than introduction of a new medication. Neonates exposed to lithium during the first trimester are at a 20-fold greater risk (0.1%) of developing Ebstein's anomaly as well as other cardiovascular malformations. These are detectable by ultrasonography as early as the 18th week of pregnancy. Evidence for later neurobehavioral sequelae in neonates exposed to lithium during the mother's pregnancy has been lacking (5). The reference by Drs. van Gent and Nabarro to "lithium poisoning" of mother and child during delivery is overstated; decreasing lithium by 50% around the estimated date of confinement is a simple and successful method of avoiding neonatal and maternal toxicity associated with diuresis and dehydration at delivery, which cause the rise in serum lithium concentration.

Managing a pregnant woman with bipolar disorder can be like "seeking to navigate the straits between Scylla and Charybdis" (6). Nonetheless, there are a number of clinical options (including lithium) with which to chart the course.

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Drs. van Gent and Nabarro Reply

SIR: Dr. Cohen and colleagues have put forward several interesting points of criticism. A number of authors (1, 2) have reported cardiovascular disorders in the fetus in the first 3 months of pregnancy following the mother's use of lithium. These authors have even found teratogenic heart disorders in 7% of these fetuses. As reported by Dr. Cohen and associates, these disorders can be detected by the ultrasound method in the 16th to 18th weeks of pregnancy. In the area of the country where we work, many people are against abortion owing to their religious beliefs. For this group of people, possible detection of disorders of the fetus does not constitute a solution to the problem.

With regard to lithium poisoning in mother and child, the chance is indeed small if, toward the end of pregnancy, the dose is reduced. It appears that a child is more sensitive to lithium than an adult; we have found one report (3), which is somewhat old, that describes symptoms of lithium intoxication in a newborn child with a lithium level of 0.32 meq/liter.

We are also aware of the antimanic effect of carbamazepine. In 1984 a 31-year-old woman who was taking lithium and wished to have children attended our policlinic. She had tried to stop taking the lithium on several occasions but had become manic immediately. She and her partner were informed of the risks involved in taking lithium and in taking carbamazepine. We also told her that we could not be certain whether her reaction to carbamazepine prophylaxis would be as favorable as her reaction to lithium had been. Nevertheless, she ultimately chose carbamazepine despite the small teratogenic risk of cleft palate (4). The patient gave birth to a healthy son while she was on the carbamazepine regimen. In the years after her son's birth, the prophylactic effect of carbamazepine did not appear to be as strong as that of lithium. The patient clearly had more mood fluctuations when she was taking carbamazepine, but she kept on taking it because of her wish to have children. Her son is now 2 years old and does not have any physical or psychological abnormalities.

The reasons why we did not prescribe carbamazepine for the patient with unipolar mania are the following. Several years earlier, a good prophylactic effect had been achieved with the use of neuroleptics. At another Dutch clinic, lithium had been prescribed because of the fear of tardive dyskinesia. Owing to our patient's faith in neuroleptics, her favorable previous response to them, and her wish to become pregnant, haloperidol was chosen. In her case also, it was not possible to discontinue the medication.

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Idiosyncratic Reaction to Naltrexone Augmented by Thioridazine

SIR: We wish to broaden the issue of a presumed adverse interaction between thioridazine and naltrexone, which was reported by Iradj Maany, M.D., and associates (1). The authors presented two cases of patients with schizophrenia who had been maintained on thioridazine for months to years; they were ultimately given naltrexone, 50–100 mg, in a pilot research protocol studying the effects of naltrexone on tardive dyskinesia. Both patients had severe lethargic reactions that lasted from 12 to 36 hours after the dose of naltrexone. The authors concluded that this was an adverse interaction between thioridazine and naltrexone.

We recently reported (2) a naltrexone trial in which depression, fatigue, energy, and other variables were assessed

in a nonpsychiatric sample of 49 obese adults (34 women and 15 men). Overall, there were no differences between the placebo and the naltrexone groups, the latter having been treated with 200 mg of naltrexone twice daily for 8 weeks. The exception was a 58-year-old white man who developed a severe reaction to naltrexone, strikingly similar to the reactions in the cases reported by Dr. Maany and colleagues. Immediately after taking his first dose of naltrexone, 100 mg, this patient began noting increasing daytime sleepiness. By 8 hours later he noted that it took great effort to move and that he felt heavy, particularly in his upper extremities. The symptoms continued, with excessive sleepiness and lethargy. After about 36 hours, he recovered.

Studies of animals indicate that endogenous opioids, as well as morphine, are involved in the activation of dopaminergic circuitry which functions in sensorimotor integration and, in particular, initiation of motor behavior (3). It has also been shown that endogenous opioids bind in varying degrees to dopamine receptor ligands (4). We propose that it is possible that naltrexone, in susceptible individuals, has an affinity for binding to specific dopamine sites that antagonize motor behavior.

We conclude that naltrexone alone can produce side effects of severe lethargy and excessive sleepiness which occur independent of an interaction with thioridazine. It is possible that this lethargy/hypersomnolence syndrome following use of naltrexone is more likely to be provoked by any combination of an antipsychotic and naltrexone. Both may enhance dopamine blockade. Although the condition seems to be rare, clinicians should be alert to this possibility.

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ALEX MORTON, PHARM.D.
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Drs. Maany and O'Brien Reply

SIR: We appreciate the comment on our letter by Dr. Malcolm and colleagues. They used a much higher dose of naltrexone in their study (200 mg b.i.d., compared to the standard dose of 50 mg/day or 100 mg every other day) (1). At such high doses naltrexone may have side effects unrelated to its opiate-blocking effects. One of their 49 subjects developed increasing daytime sleepiness and lethargy, which was similar to our cases.

On the basis of their finding, Dr. Malcolm and associates conclude that naltrexone alone can produce side effects of severe lethargy and excessive sleepiness independent of an interaction with thioridazine. Our experience with more than 600 former opioid abusers treated with naltrexone indicates that naltrexone does not generally produce sedative effects at a dose of 50 mg/day (2).

We conclude that the combination of naltrexone and thioridazine caused the extreme sedation in our patients, since either alone could not explain the symptoms.

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IRADJ MAANY, M.D.
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Comments on References to the American Board of Psychiatry and Neurology in an Article

SIR: Several points raised by Joel Yager, M.D., and Jonathan F. Borus, M.D., in their Commentary "Are We Training Too Many Psychiatrists?" (1) pertain to the American Board of Psychiatry and Neurology (ABPN) and merit a response.

On page 1042, second paragraph, the authors refer to candidates who, "presumably, completed training in accredited residency programs." We take exception to the word "presumably"; in fact, the Board scrupulously reviews all applications and goes to great lengths to review documentation of individuals' training before inviting them to sit for the examination.

On page 1046, the authors refer to a "watered-down certifying examination" and assert that the "requirements for psychiatric Board certification have been made less rather than more stringent over the years." We know of no data to support these statements. In fact, the requirements have become more stringent (in terms of PGY-1 experience, equivalent training, etc.), and the current written examination (which pays ample attention to neurology and neuropsychiatry) and oral examination (which is composed of one "live" patient interview and one videotaped patient interview) are both more standardized and more subject to ongoing study in order to improve them.

On page 1047, the authors fail to emphasize that the current process for Board certification is voluntary, and, as long as it is, training programs cannot be penalized if, say, fewer than one-third of their graduates choose to take the examination, to say nothing about passing it.

There are other matters of importance that deserve a response, but not from the ABPN: 1) the statement that "there is no guarantee that psychiatrists (or anyone else) know exactly how to intervene effectively for many psychiatric disorders"; 2) the reference concerning subspecialization by the American Board of Family Practice; 3) the implied superiority of the British system; 4) several questionable comments directed at the Residency Review Committee; and 5) the statement that the American Board of Thoracic Surgery rejects applications from candidates who have completed required training in programs where the Board failure rate has been excessively high. We understand that the article by Drs. Yager and Borus was derived from an APA annual meeting debate. Such presentations are designed to present

one side of an argument, not comprehensive balanced discussions of complex issues. This might explain the carelessness of two distinguished psychiatric educators. Perhaps the *Journal* should consider publishing a rebuttal to their argument as well.

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Drs. Yager and Borus Reply

SIR: We are pleased to have the opportunity to address the issues raised by the psychiatrists of the ABPN. The ABPN does review credentials by requiring candidates to verify their completion of accredited training. However, given the acknowledged weakness of many accredited programs, the ABPN might also assume responsibility for defining minimal standards for clinical training experience. The American Board of Thoracic Surgery has taken this responsibility in its specialty, clearly stating that "the Credentials Committee has been authorized by the Board to reject candidates from approved programs if their training is considered to be inadequate" (1).

One reason for regarding the current Board examination as "less stringent" is described in the article: the Part 2 (oral) examination formerly included two "live" psychiatric patient interviews rather than one, as is done now. Since the ability to form an alliance with and elicit data from a patient for accurate case assessment and treatment planning is a critical psychiatric skill, we believe that halving the opportunity for examiners to directly observe how candidates work with patients weakens the examination. ABPN's substitution of videotape for "live" interviews may serve the Board's logistical need to test large numbers of candidates and its laudable desire to standardize the examination; however, the disproportionate cost of this substitution is the decreased opportunity to directly assess candidates' clinical skills.

We see the continued voluntary nature of certification in all specialties as a fundamental flaw in this country's system of professional accountability. We should emulate our Canadian colleagues, who require a candidate to demonstrate clinical competence in their certifying examinations in order to practice and be reimbursed as a specialist. Our accountability would be further improved if the Residency Review Committee reviewed the certification experience of each program's graduates as one important assessment of the quality of that program's trainees and the success of its training.

Regarding the other comments, 1) we trust that the ABPN psychiatrists do not truly believe that we currently have specific, effective interventions for all psychiatric disorders. 2) The American Board of Family Practice has developed a certifying procedure for "added qualifications" in geriatrics that contains psychiatric material and will produce competitors for geriatric psychiatry patients. 3) We did not imply that the British system is superior—just that it is different, and we believe that economic forces will make our medical system more like theirs in the future. 4) The exact statement of the American Board of Thoracic Surgery has been provided.

Finally, we agree that there are many sides of these complex issues, and we recommended that the *Journal* accompany our article with an editorial presenting contrary views. Although based on our APA debate, the arguments presented in the article were carefully thought through, and many psychiatrists and manpower experts agree with our logic and conclusions. Our basic point remains that our field must improve its quality, even at the cost of decreasing its quantity. The ABPN and Residency Review Committee both have responsibilities in achieving this end. We would welcome convincing data that the nation still needs to train increasing numbers of psychiatrists; after all, as our colleagues on the Board know, we both earn our livelihoods training residents.

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Boston, Mass.

Choosing a Psychiatric Residency

SIR: We support the *Journal*'s publication of manuscripts on education and appreciate the publication of the study by William H. Sledge, M.D., and associates on applicants' choice of a residency training program (1). The results of their survey of the medical student class of 1981 with respect to factors that influenced choice of a psychiatric residency program highlight some interesting characteristics of the applicant pool. Of the 318 respondents, 63.8% ranked geography and 47.5% ranked intuitive feeling about the program among their highest four rankings out of a possible 15. A program's specific theoretical orientation (psychodynamic, biological, or social and community) was ranked much lower than the other factors under investigation.

These findings are consistent with those in a survey of the class of 1983 that we conducted, in which 13 factors that possibly influence choice of a residency were studied (2). The 254 respondents gave significantly higher ratings to three factors: satisfaction of residents currently in program, eclectic orientation, and location. The most frequently specified item was the satisfaction of the residents currently in the program (ranked "vital" by 63% of the respondents). This item is probably closely related to the factors intuitive feeling about the program and impression made by residents in the study by Dr. Sledge and associates. An eclectic orientation was rated vital by 55% of our respondents. This is consistent with a finding of the importance of electicism in a study by Weissman and Bashook (3) and the relative unimportance of

the paradigm perspectives in the study by Dr. Sledge and associates. Location (region of the country) was rated vital in program selection by 48% of the graduates in our survey.

In further support of these conclusions are the results of our survey of the class of 1984 (297 respondents) (4). Of 16 factors studied, the same three factors—satisfaction of current residents, eclectic orientation of department faculty, and geographic location—again received the highest ratings (ranked "vital" in program choice by 74%, 69.8%, and 53.8% of the respondents, respectively). These findings replicate those of our earlier study (2). In addition, this survey revealed the critically important role of the applicant's spouse or partner in choosing a residency program. Fifty-two percent of the students in our sample were married or single and cohabitating. Thirty-six percent reported that a "significant other" had very much influence in their choice of program, 34% reported some influence, and 30% reported no influence.

The results of these studies are consistent and have important implications for psychiatric educators and recruitment officers. Applicants seem to be influenced in large measure by their perceptions of the residents and faculty. Program location and broad-based training are strong determinants of program choice. In addition, for at least two-thirds of applicants, the needs of the "significant other" appear to be significant indeed. For recruiters, these findings might suggest the importance of focusing on the personal needs of applicants and making an effort to demonstrate support and interpersonal sensitivity. Liberal access to satisfied residents (assuming they are available) should be provided. Eclecticism is clearly the preferred theoretical position.

These findings also hint at the mood of today's "consumers" of psychiatric services. Medical students are neither titillated by our theoretical ruminations nor charmed by our subspecializations. They have relatively little interest in biased education or training. New medical graduates seek a sound, practical foundation in the biopsychobehavioral sciences as part of an educational process that will prepare them for advances in our field. They seem to be generally secure and trusting of their perceptions, feelings, and intuitions and are more influenced by these and other personal factors than by traditional curricular variables.

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AL SANTOS, M.D.
BEN SAUNDERS, PH.D.
JOHN ROBERTS, M.D.
Charleston, S.C.

Dr. Sledge and Associates Reply

SIR: We commend the work of Dr. Santos and his colleagues, which is consistent with our findings and suggests that the phenomenon of resident applicants' interest in broad-based training and noncurricular, personal matters is consistent over several years. We are curious whether applicants seeking psychiatric training are different along these dimensions from those entering other specialities. There are suggestions that medical school graduates fall into two large categories: those who are patient oriented and those who are disease oriented (1). If this is so, it seems logical to suppose that psychiatry tends to attract a greater proportion of patient-oriented applicants, who may pay more attention to broad-based training and personal issues that are not related to the training program per se.

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WILLIAM SLEDGE, M.D.
PHILIP J. LEAF, PH.D.
New Haven, Conn.
MICHAEL H. SACKS, M.D.
New York, N.Y.

Atropine Coma in Treatment of Opiate Addiction

SIR: L. Wandzel, M.D., and Z. Falicki, M.D., Ph.D., reported in this journal (1) that atropine is a possible treatment for opiate addiction. This is consistent with the pharmacology of opiates.

Signs and symptoms of opiate withdrawal, including coryza, sialorrhea, nausea, vomiting, anorexia, diarrhea, myalgias, sleepiness, anxiety, agitation, irritability, headaches, dizziness, tachycardia, and hypertension, can be produced by anticholinesterases (2). Narcotic agonists block the release of acetylcholine from guinea pig cortex and ileum (3–5). This effect is mediated through an action of opiates on presynaptic cholinergic neurons. A secondary effect may be a shift to the left in the dose-response curve for the production of symptoms by acetylcholine. This would occur if opiates supersensitize cholinoceptive neurons, which would create a pathophysiologic basis for the development of a cholinergic overdrive state upon the withdrawal of opiates. It is noteworthy that many of the symptoms mentioned in the report by Drs. Wandzel and Falicki are apt to occur in subjects challenged with anticholinesterases.

The literature summarizing the cholinergic effects of substances of abuse was recently reviewed (6). Cannabis, ethanol, and barbiturates also inhibit the release of acetylcholine. Interestingly, antimuscarinic agents are also liable to be abused. Thus, five classes of drugs that diminish the interaction of acetylcholine with the postsynaptic muscarinic receptor are subject to abuse. Perhaps this potentially unifying effect of these drugs has been underexamined.

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STEVEN C. DILSAVER, M.D.
Ann Arbor, Mich.

Dr. Wandzel Replies

SIR: In my opinion, Dr. Dilsaver has not noticed two very important aspects of our case report. The acute withdrawal symptoms that he mentions were present in Ms. A during the first days of her hospitalization in our department. We started with her atropine coma treatment about 1 month later, when those acute withdrawal symptoms were completely absent. We used atropine coma for treatment of the mental drug dependence, not treatment of acute withdrawal symptoms.

We also want to emphasize the fact that the patient was aroused from the atropine coma after 3 hours by means of an intravenous injection of neostigmine, which has pharmacological effects that are mostly different from those of atropine. I think that the pharmacological effects of atropine coma treatment are more complicated than Dr. Dilsaver suggests.

LESZEK WANDZEL, M.D.
Bialymstoku, Poland

Freud in Context: What Do Women/Men Want?

SIR: "What does woman want?" is one of Freud's most controversial and perhaps misunderstood utterances. It has been used to indicate his inability to understand women. We might ask what Freud actually meant. "What does woman want?" is not from the text of any of Freud's scientific papers about the psychology of women. It is found in Jones's biography. Freud said once to Marie Bonaparte, "The great question that has never been answered and which I have not yet been able to answer, despite my thirty years of research into the feminine soul, is 'What does a woman want?' " [the original German, "Was will das Weib?" is given in a footnote] (1, p. 421). Jones translated the universal "woman" as the more petulant "a woman." He did not specify a date or say whether Marie Bonaparte quoted from conversation, her analysis, or a letter (2). She was Freud's analysand, pupil, and close friend and was deeply interested in the psychology of women. It was to her that Freud lamented, "What does woman want?"

Is it possible that he was joking, in the meaningful way that he understood jokes? Was he, as he did so frequently, referring to a shared literary reference? He read widely, delighted in quotations, and shared them playfully with friends. His collected letters (3) are full of literary references. There *is* one that Freud could have been citing. Perhaps he was restating in reverse Hermione Hushabye's impassioned (and unanswered) question at the end of act 1 of George Bernard Shaw's *Heartbreak House* (4): "What do men want?"

Had Freud read *Heartbreak House*? He knew other plays by Shaw and frequently quoted this playwright in both his papers and his letters. *Heartbreak House*, written in 1916–1917, had its premiere in New York in 1920 and in London in 1921. By 1924, the year Freud met Marie Bonaparte, the text would have been available.

The two questions reflect and complete each other. A man asks, "What does woman want?" A woman asks, "What do men want?" Hermione Hushabye describes men's envy of women, particularly their ability to bear children: "What do men want? They have their food, their firesides, their clothes mended, and our love at the end of the day. Why are they not satisfied? Why do they envy us the pain with which we bring them into the world, and make strange dangers and torments for themselves to be even with us?" (4, p. 515)

Freud's question, taken as a mirror image of Shaw's query, suggests a parallel between men's envy of women and women's envy of men. Together, the two questions comment on the difficulties and mysteries inherent in the human condition for both sexes.

It is intriguing to imagine that Freud had Shaw in mind and expected Marie Bonaparte to hear Hermione Hushabye's speech implicitly in his quip! (Did she?) In the meantime, perhaps it is an error to take Freud's question out of context and to use it as evidence of a bias against women.

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LYNN WHISNANT REISER, M.D.
New Haven, Conn.

Research Fever

SIR: I am writing to inform readers of the recent identification of the disease "research fever," which frequently affects certain groups of physicians and other health professionals. It is caused by a rare slow virus known as research virus, which has a predilection for members of the medical field. Its characteristics are as follows.

The research virus is found worldwide, but it is more prevalent in the Western Hemisphere and is most often identified in university and Veterans Administration hospitals in large metropolitan areas. The modal age at onset of research fever is young adulthood. Onset has not yet been reported in persons over age 50. Typically, it is first contracted in residency; occasionally, this illness begins during the medical school years. A few adolescent cases have been reported. The disease is more common in men by a ratio of 10:1. Relative immunity in women is alternatively attributed to cultural factors, endocrine influences, or both.

In the early stages, the patient is more curious than his colleagues and isolates himself in the library (often working late hours), reading journals and doing literature searches. As the disease becomes full-blown, the patient rejects lucrative job offers in favor of an academic career with decidedly less pay. In fact, the latter is *the* pathognomonic sign of research virus infection. In the differential diagnosis, research

fever should not be confused with phobic fear of entering private practice, characterologically lazy avoidance of clinical responsibilities, and fetishistic attachment to glossy paper.

Preliminary in vitro cultures and human trials have established that the only effective specific treatment is *money* offered, mailed, or inserted in the palm of the dominant hand, which provides a robust grasp reflex. Some success has been seen with time deprivation due to service or family demands. The latter have particularly unpleasant side effects.

Research fever is usually fatal when complicated by events such as publication, awards, and seeing one's name in print. However, full remissions occur about 40% of the time with vigorously administered infusions of money or frequent on-call assignments.

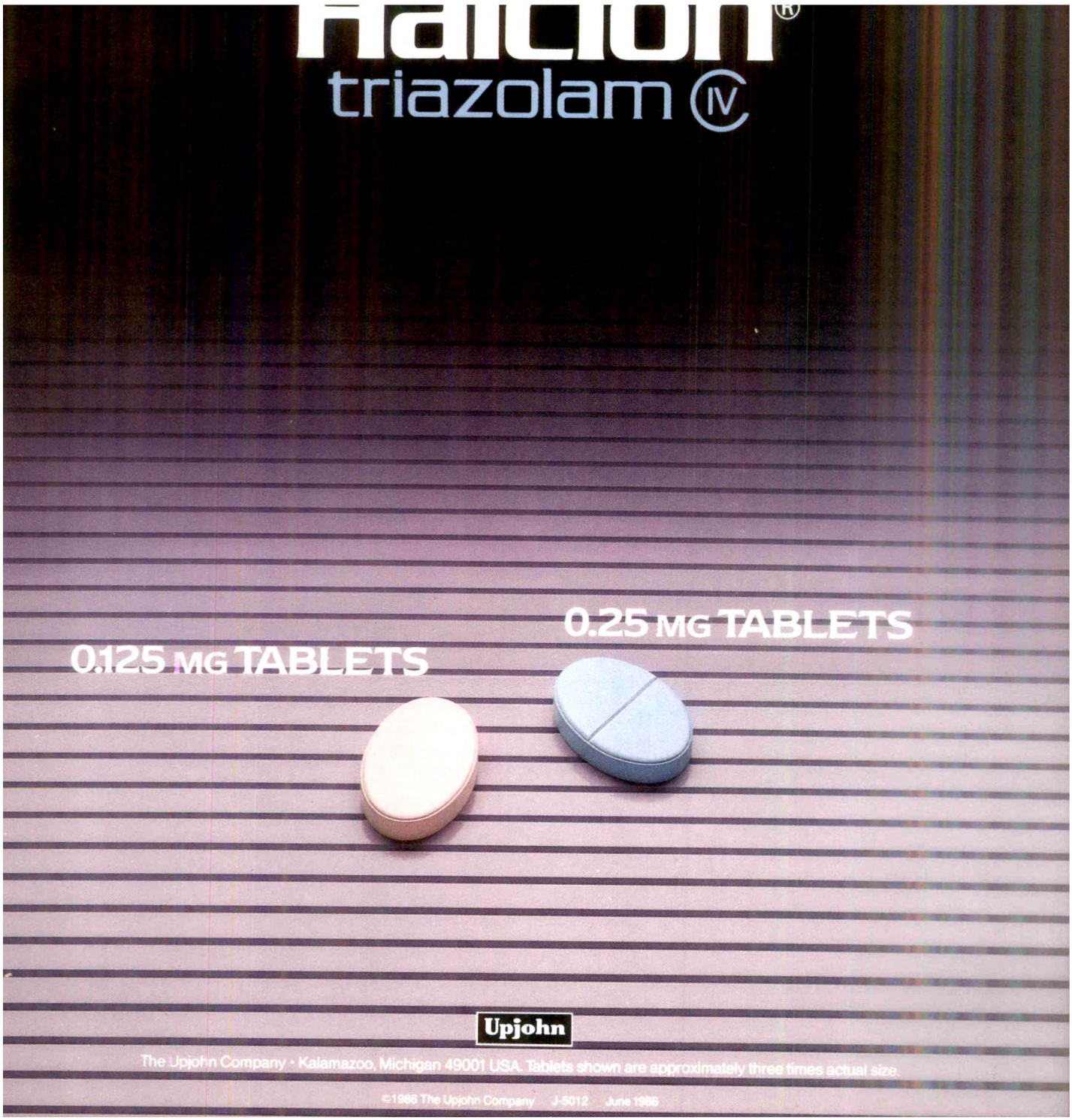
Note. Frederick S. Sierles, M.D., whose familiarity with virology extends little beyond the common cold, nevertheless reviewed and commented on this communication.

NUTAN VAIDYA, M.D.
North Chicago, Ill.

Reprints of letters to the Editor are not available.

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*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate
Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

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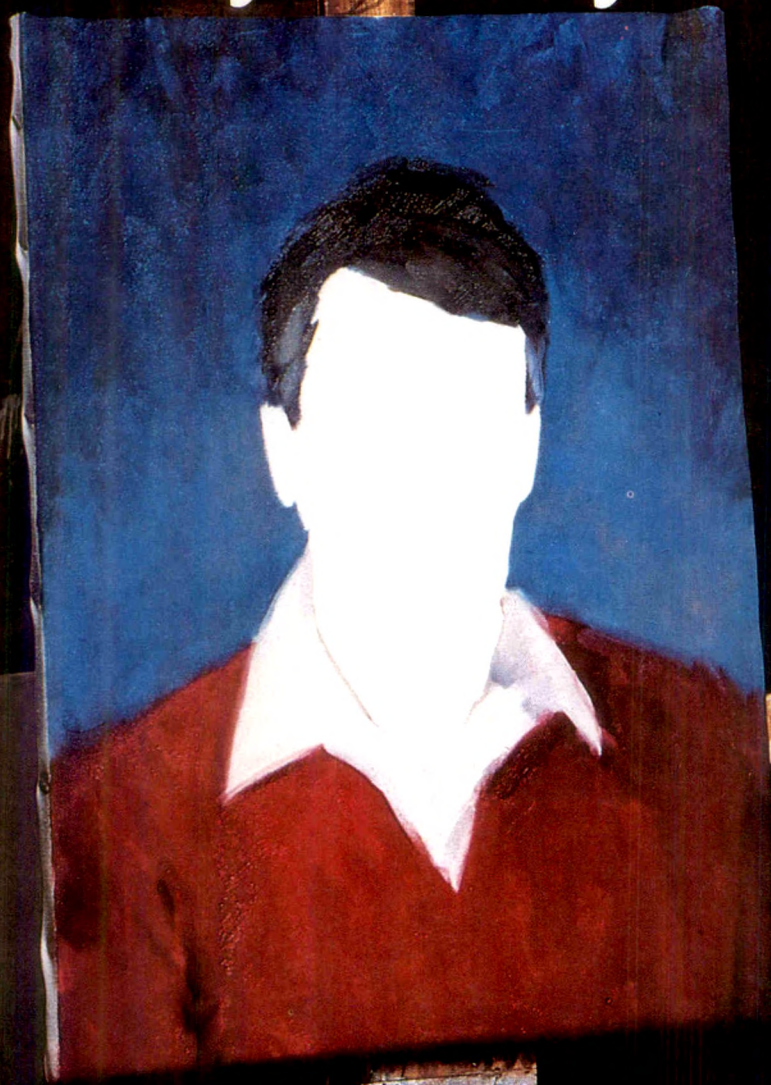
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INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coord ation, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

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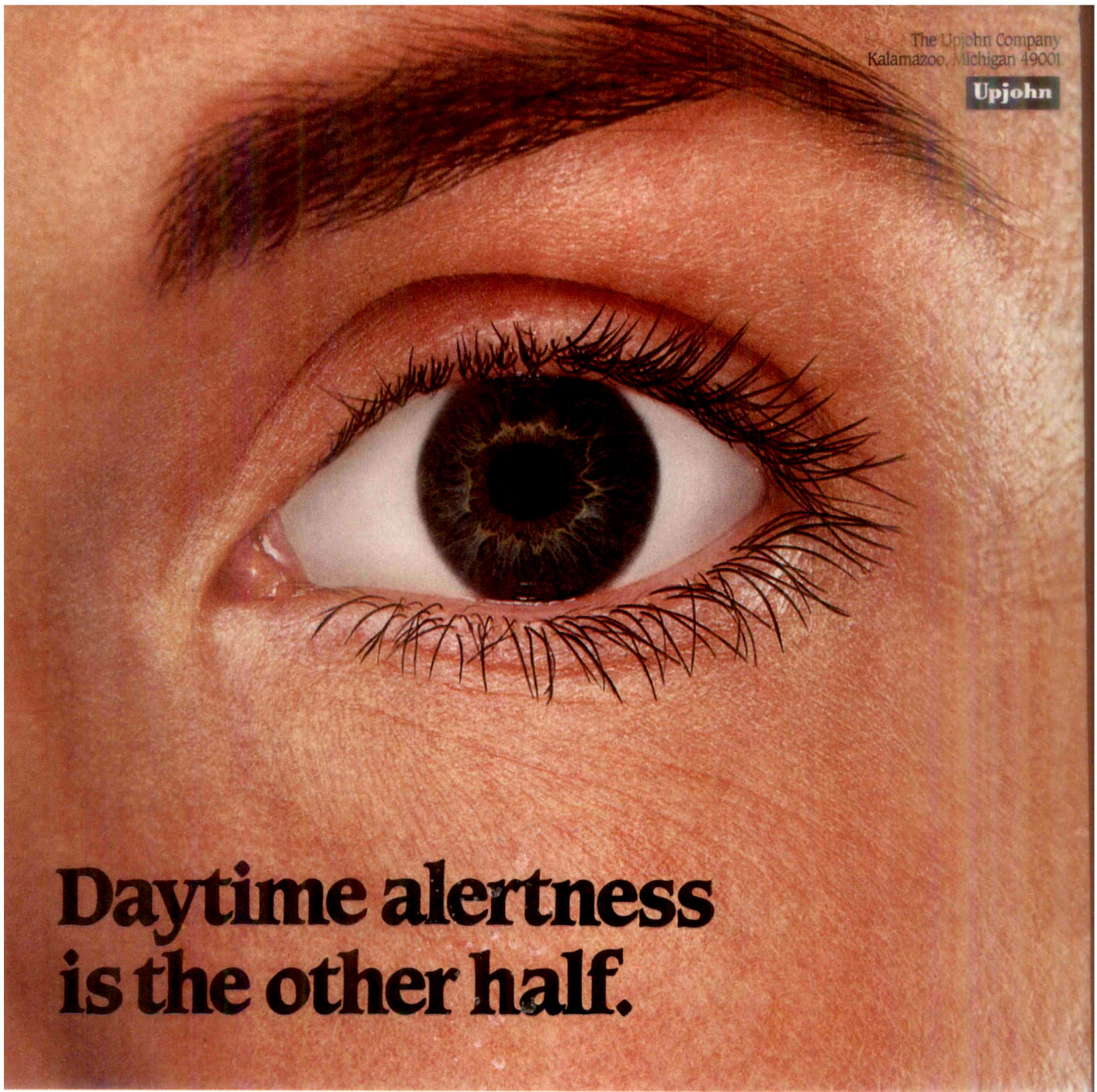
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These studies suggest that HALCION is effective adjunctive therapy for the relief of short-term insomnia in depressed patients.

Intentional overdosage of psychotropic medication is more common in depressed patients. Therefore, the least amount of medication that is feasible should be available at any one time.

The recommended dose for most adults is 0.25 mg before retiring. In geriatric and/or debilitated patients, therapy should be initiated at 0.125 mg.

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CONTRAINDICATIONS: Patients with known hypersensitivity to this drug or other benzodiazepines. HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: *General:* In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Some side effects, including drowsiness, dizziness, lightheadedness, and amnesia, appear to be dose related.

Some evidence suggests that confusion, bizarre or abnormal behavior, agitation, and hallucinations may also be dose related, but this evidence is inconclusive. It is recommended that therapy be initiated at the lowest effective dose. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin approximately doubled the elimination half-life and plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. *Nursing Mothers:* Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of HALCION and other benzodiazepines: Amnestic symptoms, confusional states, dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Other events reported include: Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, aggressiveness, falling, somnambulism, inappropriate behavior, and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30° C (59°-86° F).

Caution: Federal law prohibits dispensing without prescription. B-4-S

References:

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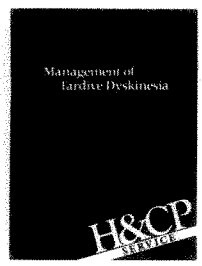
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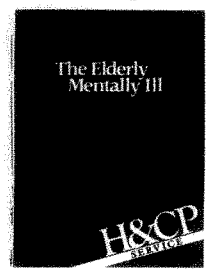
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Tardive Dyskinesia



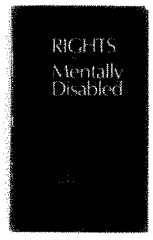
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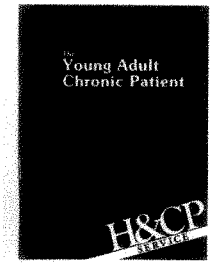
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Responsibility for the Control of Violence
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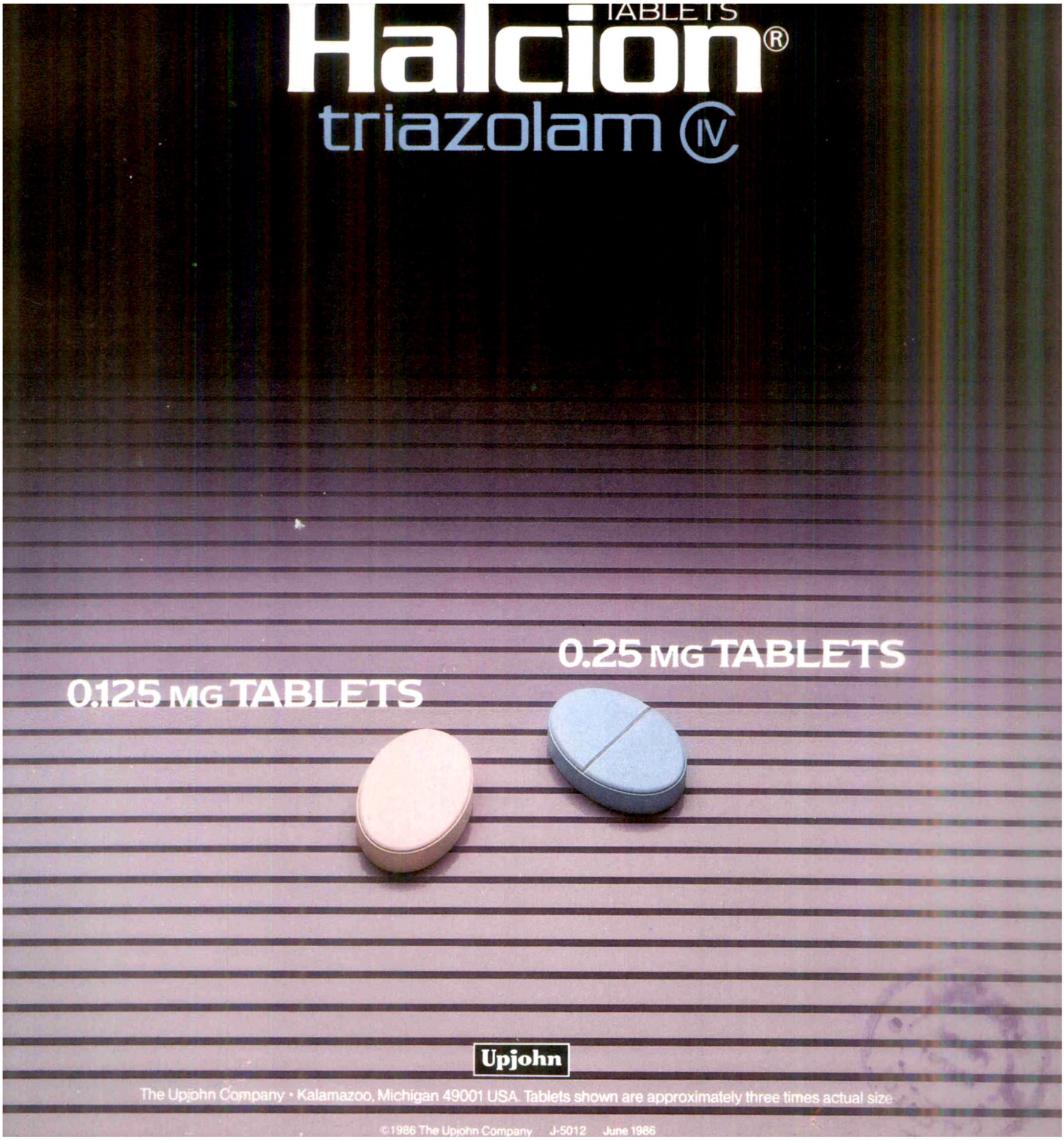
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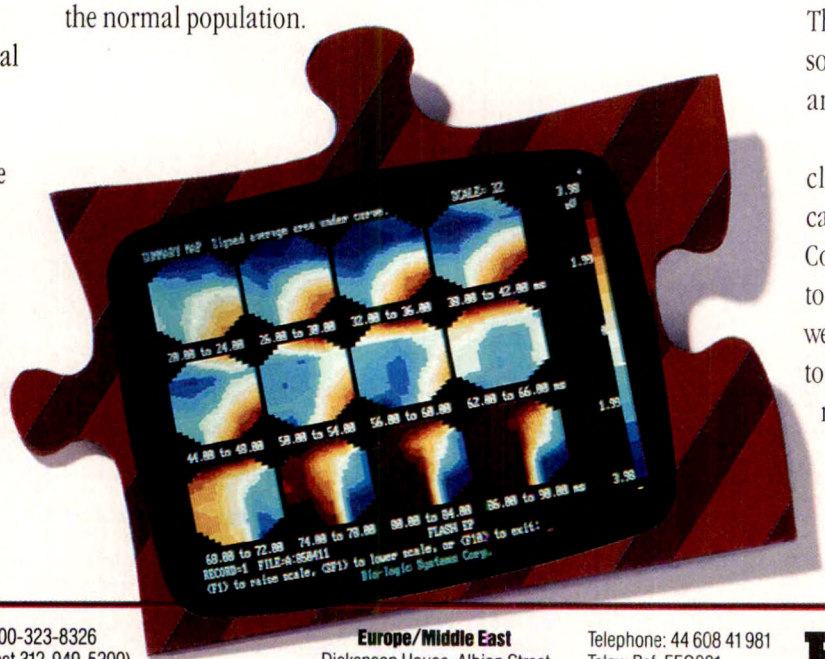
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SPECIAL ARTICLES

779 The New Preventive Detention: Psychiatry's Problematic Responsibility for the Control of Violence *Paul S. Appelbaum*

786 The *DSM-III-R* Personality Disorders: An Overview *Thomas A. Widiger, Allen Frances, Robert L. Spitzer, and Janet B.W. Williams*

796 Supervision and Privacy in Psychotherapy Training *R. William Betcher and Norman E. Zinberg*

REGULAR ARTICLES

804 Possible Role of Antidepressants in Precipitating Mania and Hypomania in Recurrent Depression *David J. Kupfer, Linda L. Carpenter, and Ellen Frank*

809 The Amphetamine Challenge Test in Patients With Borderline Disorder *S. Charles Schulz, Jack Cornelius, Patricia M. Schulz, and Paul H. Soloff*

815 The Epidemiology of Dysthymia in Five Communities: Rates, Risks, Comorbidity, and Treatment *Myrna M. Weissman, Philip J. Leaf, Martha Livingston Bruce, and Louis Florio*

820 Ventricular and Sulcal Size at the Onset of Psychosis *William G. Iacono, Geoffrey N. Smith, Margaret Moreau, Morton Beiser, Jonathan A.E. Fleming, Tsung-yi Lin, and Borys Flak*

825 The Revision of Axis V in *DSM-III-R*: Should Symptoms Have Been Included? *Andrew E. Skodol, Bruce G. Link, Patrick E. Shrout, and Ewald Horwath*

830 Foundation Funding and Psychiatric Research *Diana Kim, Harold Alan Pincus, and Theodora Fine*

836 A Curriculum for Education in Geriatric Psychiatry *Robert S. Marin, Jeffrey R. Foster, Charles V. Ford, Burton V. Reifler, Barry Reisberg, Carolyn B. Robinowitz, William H. Sledge, James Spar, and Patti J. Tighe*

COMMENTARY

844 Graphic Representation of the Life Course of Illness in Patients With Affective Disorder *Robert M. Post, Peter P. Roy-Byrne, and Thomas W. Uhde*

BRIEF COMMUNICATIONS

849 Effect of Psychosis on Suicide Risk in 1,593 Patients With Unipolar and Bipolar Affective Disorders *Donald W. Black, George Winokur, and Amelia Nasrallah*

853 Quantitative Magnetic Resonance Imaging and the Severity of Dementia in Alzheimer's Disease *William Bondareff, Janak Raval, Patrick M. Colletti, and Douglas L. Hauser*

857 Reliability of Psychiatric Scales in Patients With Dementia of the Alzheimer Type *Gary L. Gottlieb, Raquel E. Gur, and Ruben C. Gur*

861 Alpha Frequency in Schizophrenia: An Association With Enlarged Cerebral Ventricles *Craig N. Karson, Richard Coppola, and David G. Daniel*

865 Combat-Related Posttraumatic Stress Disorder Among Second-Generation Holocaust Survivors: Preliminary Findings *Zahava Solomon, Moshe Kotler, and Mario Mikulincer*

869 Drug-Induced Dystonia in Young and Elderly Patients *Gerard Addonizio and George S. Alexopoulos*

872 Who Seeks Mental Health Care in China? Diagnoses of Chinese Outpatients According to *DSM-III* Criteria and the Chinese Classification System *Lori L. Altshuler, Wang Xida, Qi Haiqing, Hua Qian, Wang Weiqi, and Xia Meilan*

CLINICAL AND RESEARCH REPORTS

876 Lack of Association Between HLA Antigens and Anorexia Nervosa *Alexander Kiss, Agathe Hajek-Rosenmayr, Alexander Haubenstock, Stefan Wiesnagrotzki, and Gabriele Moser*

878 Exacerbation of Psychosis After Discontinuation of Carbamazepine Treatment *C.W. Chris Heh, John Sramek, John Herrera, and Jerome Costa*

880 ECT-Induced Postictal Delirium and Electrode Placement *Ismael Leechuy, Richard Abrams, and Joanne Kohlhaas*

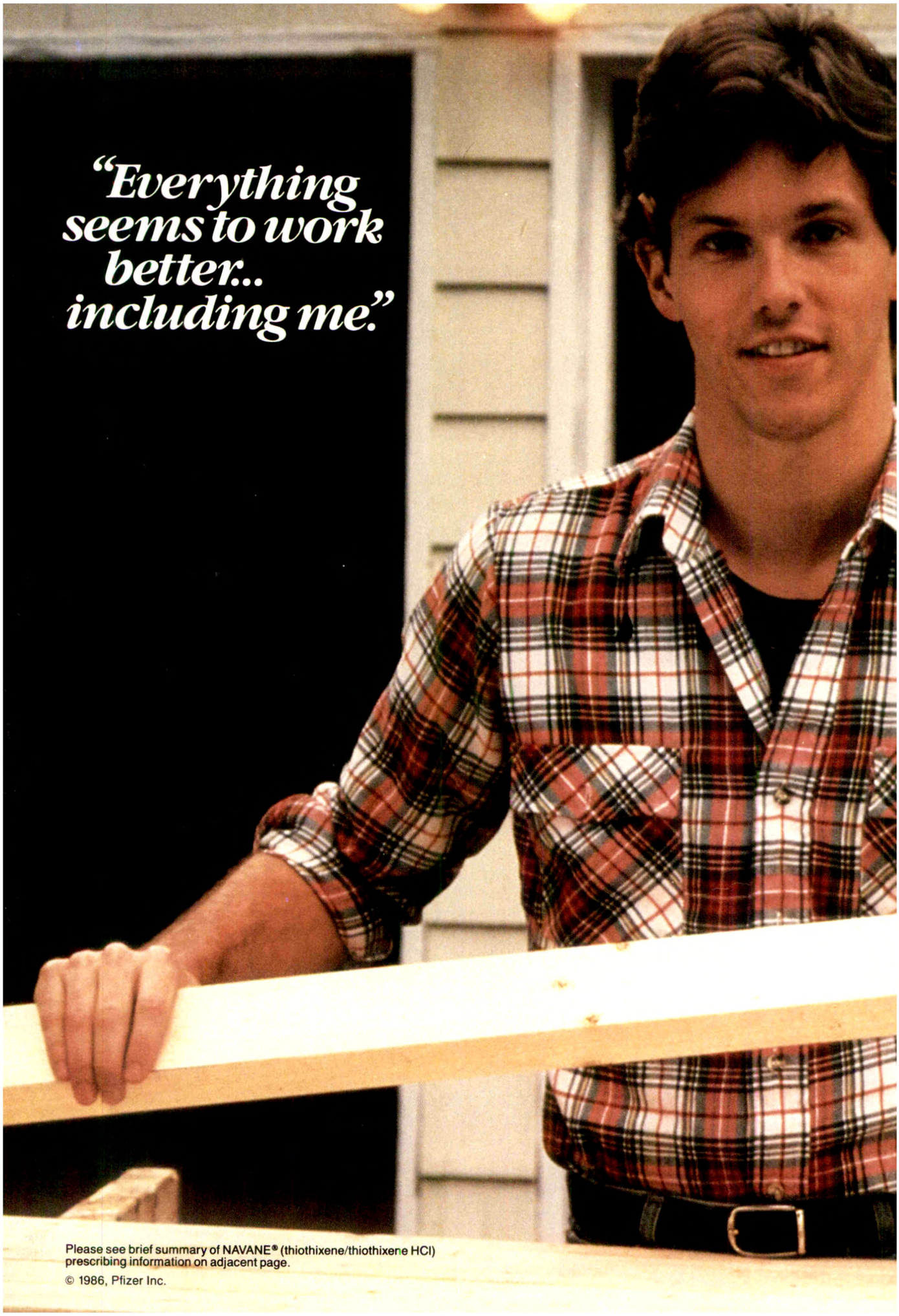
882 Prevalence of Clinically Significant Depressive Symptoms in Black and White Patients in Family Practice Settings *William W.K. Zung, James MacDonald, and Elizabeth M. Zung*

BOOK FORUM 884

LETTERS TO THE EDITOR 895

OTHER

803 Deceased Members of the American Psychiatric Association
A11 Calendar
A15 Books Received
A23 Officers of the American Psychiatric Association
A36 Index to Advertisers
A37 Information for Contributors
A41 *British Journal of Psychiatry* Contents



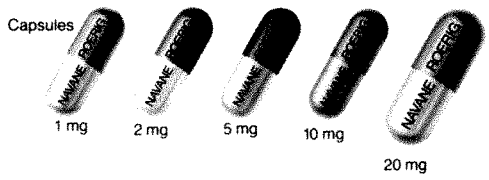
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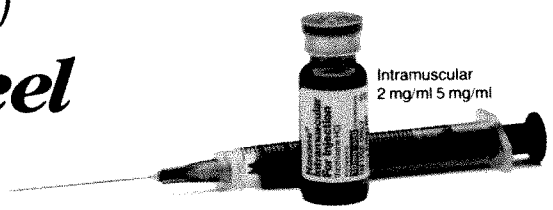
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Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.
Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.
Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.
Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

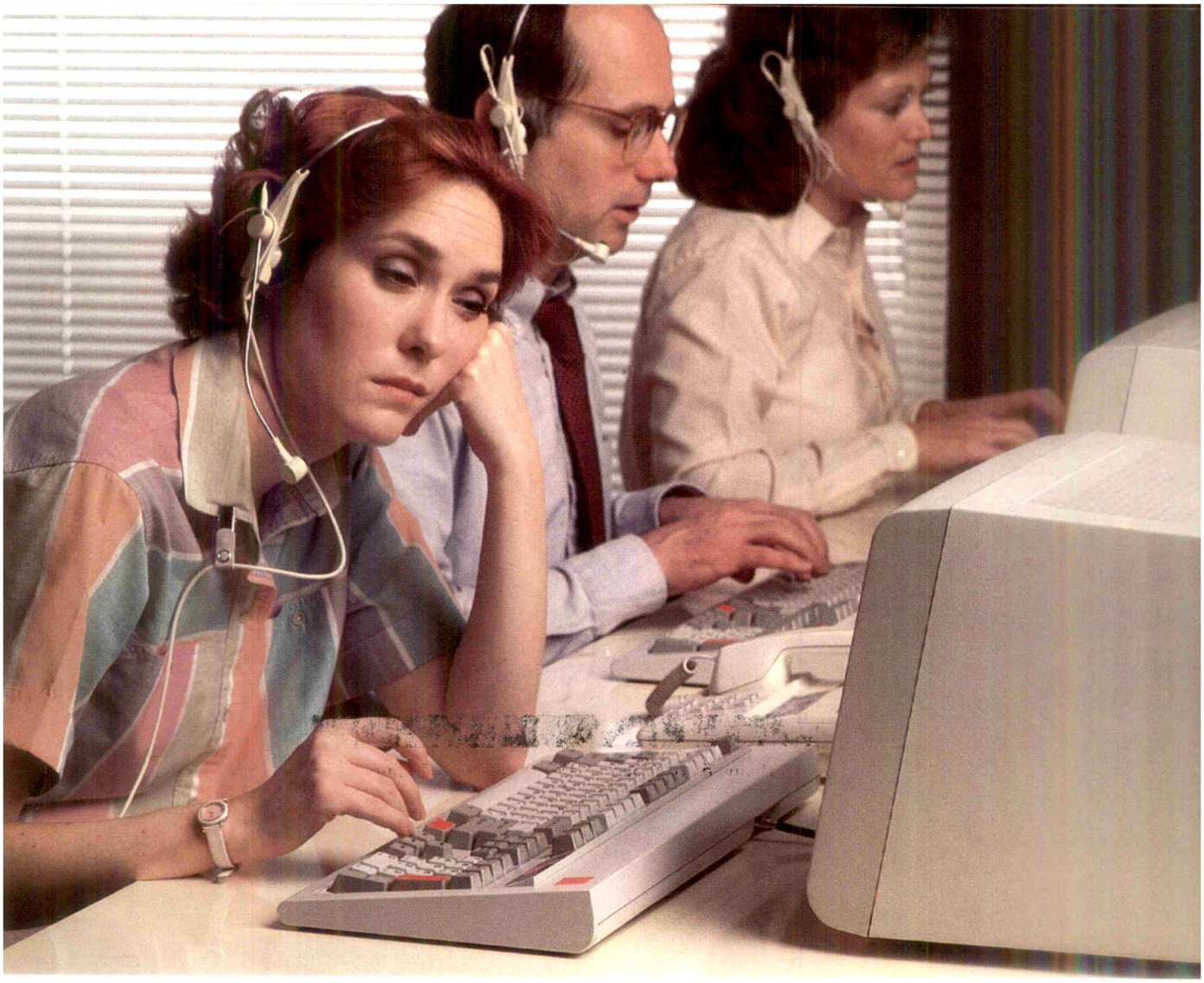
Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.
Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.
Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

ROERIG Pfizer
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Asleep at the switch. This calls for a switch in antidepressants.

With PAMELOR there is little daytime sedation. Yet all the efficacy of amitriptyline.

When patients with depression are being treated with PAMELOR, they're able to keep operating on all circuits.

That's because PAMELOR works as effectively as amitriptyline,[1] yet doesn't keep your patient from working. Daytime sedation is low[2-4]; consequently, patient productivity can remain high.

What's more, PAMELOR has a low incidence of anticholinergic[2,3] and hypotensive[2,3,5-7] side effects. So, for those patients on another antidepressant, a switch to PAMELOR therapy could help across the board.

PAMELOR may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating heavy machinery or driving a car; therefore, the patient should be warned accordingly. Because of anticholinergic activity, PAMELOR should be used with caution in patients who have glaucoma or a history of urinary retention. As with all antidepressants, patients with cardiovascular disease should be given PAMELOR only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time.

PAMELOR®
(nortriptyline HCl)
The active metabolite of amitriptyline

For Brief Summary, please see following page.

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PAM 1087-12

PAMELOR®
(nortriptyline HCl)

The active metabolite of amitriptyline



10 mg/5 ml 10 mg 25 mg 50 mg 75 mg

All the efficacy of amitriptyline[1] and

- low incidence of anticholinergic side effects[2,3]
- little daytime sedation[2-4]
- low incidence of orthostatic hypotension[2,3,5-7]

References: 1. Ziegler VE, Clayton PJ, Biggs JT: A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry* 1977;34:607-612. 2. Thompson TL, Thompson WL: Treating depression: Tricyclics, tetracyclics, and other options. *Modern Medicine* 1983;51(8):87-109. 3. Georgotas A: Affective disorders: Pharmacotherapy, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry IV.* Baltimore, Williams & Wilkins, 1985, vol 1, pp 821-833. 4. Bye C, Clubley M, Peck AW: Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol* 1978;6:155-161. 5. Roose SP, Glassman AH, Siris SG, et al: Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: A meaningful difference. *J Clin Pharmacol* 1981;1:316-319. 6. Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 413-423. 7. Thayssen P, Bjerre M, Kragh-Sorensen P, et al: Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology* 1981;74:360-364.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, par thesias of extremities; incoordination, ataxia, tremors; periph neuropathy; extrapyramidal symptoms; seizures, alteration in E patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, assc ated sublingual adenitis; blurred vision, disturbance of accommo tion, mydriasis; constipation, paralytic ileus; urinary retenti delayed micturition, dilation of the urinary tract. *Allergic*—Skin ra petechiae, urticaria, itching, photosensitization (avoid excess exposure to sunlight); edema (general or of face and tongue), di fever, cross-sensitivity with other tricyclic drugs. *Hematologic* Bone-marrow depression, including agranulocytosis; eosinophi purpura; thrombocytopenia. *Gastrointestinal*—Nausea and von ing, anorexia, epigastric distress, diarrhea, peculiar taste, stomati abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in male, breast enlargement and galactorrhea in the female; increasec decreased libido, impotence; testicular swelling; elevation or depr sion of blood sugar levels; syndrome of inappropriate ADH (ar diuretic hormone) secretion. *Other*—Jaundice (simulati obstructive), altered liver function; weight gain or loss; perspirati flushing; urinary frequency, nocturia; drowsiness, dizziness, wea ness, fatigue; headache; parotid swelling; alopecia. *Withdra Symptoms*—Though these are not indicative of addiction, abr cessation of treatment after prolonged therapy may produce naus headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restles ness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperact reflexes, tachycardia, ECG evidence of impaired conduction, sho congestive heart failure, stupor, coma, and CNS stimulation with cc vulsions followed by respiratory depression. Deaths have occurr with drugs of this class. No specific antidote is known; general su portive measures are indicated, with gastric lavage. [PAM-Z13—7/15/

PAM-1087-12

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Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of greatest interest to* Journal *readers will be included.*

SEPTEMBER

September 4–7, International Congress on Forensic Sciences, Beijing, People's Republic of China. Contact China Express Congress Ltd., 1201-2 Energy Plaza, 92 Granville Rd., Tsimshatsui East, Kowloon, Hong Kong; 3-7217689; Telex 40465 CXFTN HX.

September 4–9, 10th International Congress on Criminology, Hamburg, F.R.G. Contact Congress Secretariat, HMC Congress Organisation, 10th Int. Congr. Crimin., P.O. Box 30 24 80, D–2000 Hamburg 36, F.R.G.; 040-35-69-22-42; Telex 212 609, Telefax 35 69 21 80.

September 4–9, 17th European Conference on Psychosomatic Research, Marburg, West Germany. Contact Prof. Dr. med. Wolfram Schuffel, Psychosomatic Division, Centre of Internal Medicine, University of Marburg, D-2550 Marburg, West Germany.

September 5–10, Behaviour Therapy World Congress '88, Edinburgh. Contact Rod Holland, Congress Coordinator, Congress Workshops, WCBT '88, 59 Heath Gardens, Twickenham, Middlesex TW1 4LY, England UK.

September 7–11, Fall Components Meeting, American Psychiatric Association, Washington, D.C.

September 12–17, IVth International Conference of Psychophysiology, Prague. Contact Association of Czechoslovak Medical Societies, J.E. Purkyne, IVth I.C.P., P.O. Box 88, CS–120 26 PRAHA 2, Czechoslovakia; Telex 121293.

September 14–17, Fourth International Conference of the Marce Society, The Family, Childbearing and Mental Illness, University of Keele, England. Contact Marce Society Secretariat, Bell Howe Conferences, Gothic House, Barker Gate, Nottingham, NG1 1JU, England; 0602-410679.

September 14–17, IX International Symposium on the Psychotherapy of Schizophrenia, Torino, Italy. Contact Organizing Secretariat — IMC S.r.l., Via S. Quintino 28, 10121 Torino, Italy; 011-51-54-21; Telex 220533 GALIL I; Telefax 518612.

September 17, International Symposium on Sleep Disorders, Sao Paulo, Brazil. Contact Rubens Reimao, M.D., Rue Glicineas 128, 04048 Sao Paulo, SP, Brazil.

September 21–23, II Panamerican Sleep Congress, Buenos Aires. Contact Enrique Soltanik, M.D., Jufre 1 , 14 4) Buenos Aires, Argentina.

September 22, interim meeting, American Board Medical Specialties, Chicago. Contact Donald G. Langsley, M.D., Executive Vice-President, One American Plaza, ite 805, Evanston, IL 60201; 312-491-9091.

September 23–25, child psychiatry examination, American Board of Psychiatry and Neurology, Washington, D.C. Contact Stephen C. Scheiber, M.D., Executive Secretary, ABPN, 500 Lake Cook Rd., Suite 335, Deerfield, IL 60 15, 312-945-7900.

September 23–26, annual meeting, Royal College of Physicians and Surgeons of Canada, Ottawa. Contact Dr. J.H. Darragh, Executive Director, 74 Stanley Ave., Ottawa, Ontario, Canada K1M 1P4; 613-746-8177.

September 25–28, annual meeting, Alcohol and Drug Problems Association of North America, Inc., Charlotte, N.C. Contact Karst J. Besteman, Executive Director, 444 N. Capitol St., N.W., Suite 181, Washington, DC 20001 02-737-4340.

September 25–28, annual meeting, Association Mental Health Administrators, St. Louis. Contact Laurie Pool, Director, 840 North Lake Shore Dr., Suite 1103W, Chicago, IL 60611; 312-943-2751.

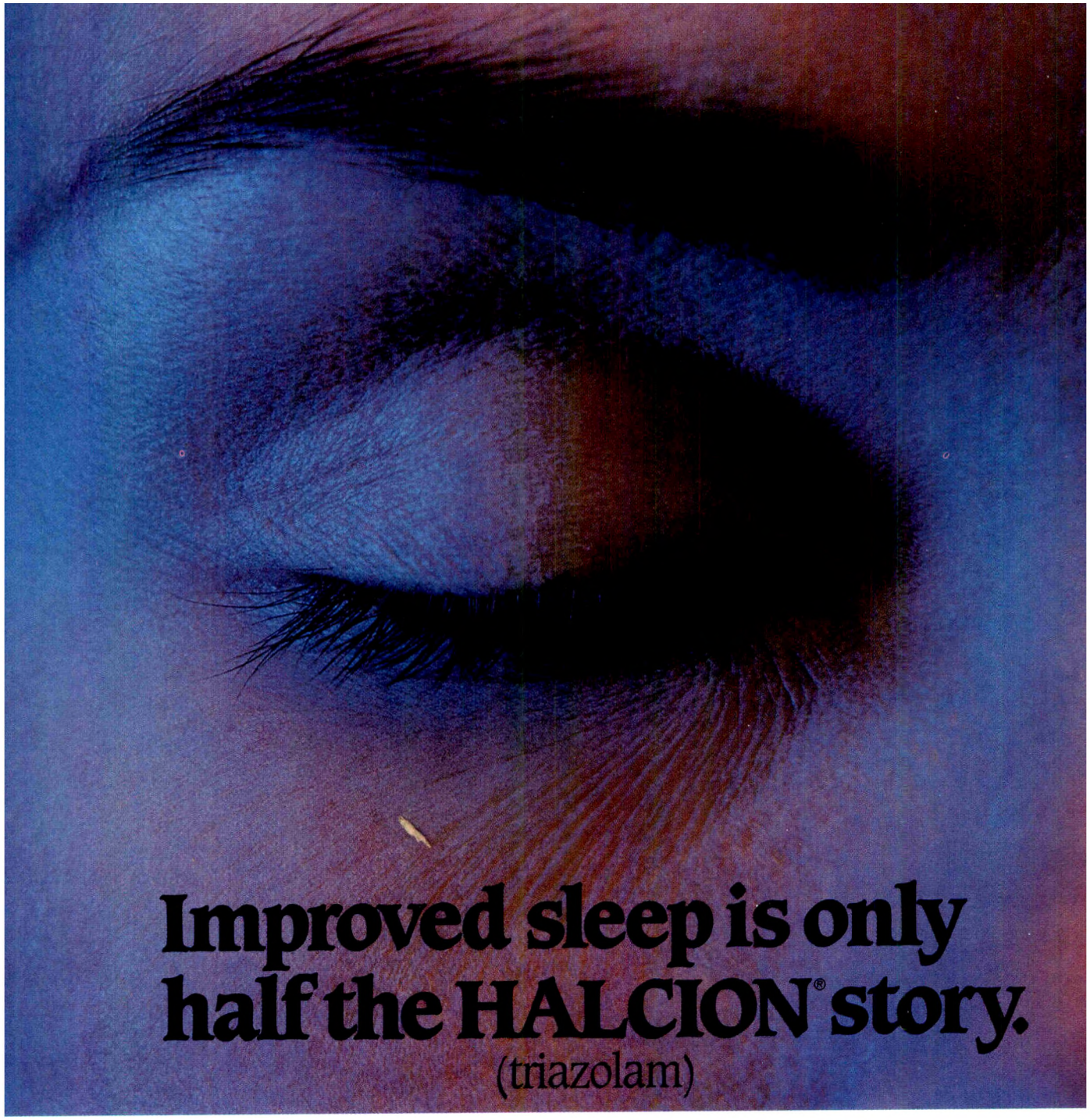
September 26–29, annual meeting, American College of Emergency Physicians, New Orleans. Contact Col C. Rorrie, Jr., Ph.D., Executive Director, P.O. Box 6199 , Dallas, TX 75261-9911; 214-550-0911.

September 26–29, annual meeting, World Medical Association, Vienna. Contact Angel Orozco, Executive Director, 28, Avenue des Alpes, 01210 Ferney-Voltaire, France; 40-75-75.

September 28–30, annual meeting, Canadian Psychiatric Association, Halifax, Nova Scotia, Canada. Contact Lea G. Metivier, Chief Administrative Officer, 294 Albert St., Suite 204, Ottawa, Ontario, Canada K1P 6E6; 613-23 2815.

September 28–October 1, annual meeting, American School Health Association, Lake Buena Vista, Fla. Contact Dena A.

(Continued on page A-20)



Improved sleep is only half the HALCION® story.

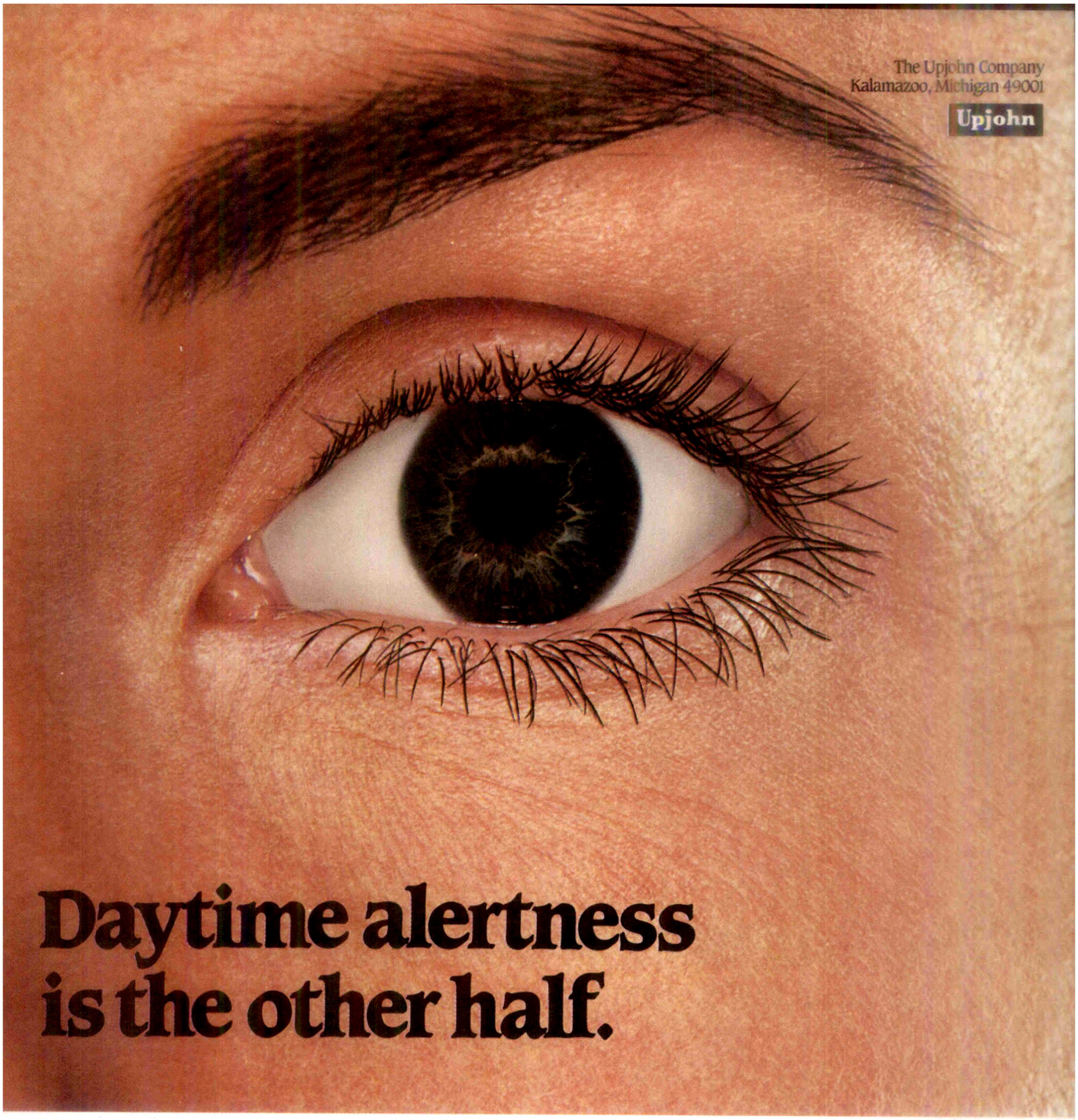
(triazolam)

In depressed patients HALCION is effective when adjunctive insomnia therapy is required.

Disturbed sleep is not an uncommon problem in depressed patients, and although standard tricyclic antidepressants (TCAs) usually relieve insomnia, some depressed patients continue to experience its symptoms. The short-term use of HALCION to relieve insomnia refractory to treatment with TCAs has proven successful in two clinical evaluations.

Effective, concomitant therapy.

HALCION was compared with placebo in a double-blind comparative study of 53 depressed outpatients who had been stabilized on a TCA for at least six weeks but who still suffered refractory insomnia. HALCION was shown to be more effective in relieving the symptoms of insomnia without making depressive symptoms worse.[1]



In another double-blind study comparing HALCION with placebo in 78 depressed outpatients receiving 50-300 mg of imipramine per day, HALCION was significantly more effective in improving most sleep parameters. In addition, there was no evidence that HALCION interfered with the efficacy of imipramine or aggravated the patients' depressive symptoms.[2]

These studies suggest that HALCION is effective adjunctive therapy for the relief of short-term insomnia in depressed patients.

Intentional overdosage of psychotropic medication is more common in depressed patients. Therefore, the least amount of medication that is feasible should be available at any one time.

The recommended dose for most adults is 0.25 mg before retiring. In geriatric and/or debilitated patients, therapy should be initiated at 0.125 mg.

0.125 & 0.25 MG TABLETS

Halcion®

triazolam (IV)

Helps meet both goals of insomnia therapy

Please see adjacent page for prescribing information.

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Halcion® Tablets (triazolam) ℞

INDICATIONS AND USAGE: HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS: Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: *General:* In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Some side effects, including drowsiness, dizziness, lightheadedness, and amnesia, appear to be dose related.

Some evidence suggests that confusion, bizzare or abnormal behavior, agitation, and hallucinations may also be dose related, but this evidence is inconclusive. It is recommended that therapy be initiated at the lowest effective dose. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin approximately doubled the elimination half-life and plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. *Nursing Mothers:* Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of HALCION and other benzodiazepines: Amnestic symptoms, confusional states, dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Other events reported include: Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, aggressiveness, falling, somnambulism, inappropriate behavior, and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription. B-5-S

References:

1. Cohn JB: Triazolam treatment of insomnia in depressed patients taking tricyclics. *J Clin Psychiatry* 1983;44(11):401-406.
2. Dominguez RA, Jacobson AF, Goldstein BJ, et al: Comparison of triazolam and placebo in the treatment of insomnia in depressed patients. *Curr Ther Res* 1984;36(5):856-865.

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J-9507
June 1988

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Psychoanalytic Psychotherapy in an
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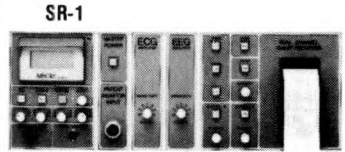
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- Printed record of treatment and self test
- Printed record of stimulus parameters
- Modular design for maximum flexibility

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Books Received

Hypochondria: Woeful Imaginings, by Susan Baur. Berkeley, University of California Press, 1988, 247 pp., $19.95.

Behavioral Assessment: A Practical Handbook, 3rd ed., edited by Alan S. Bellack and Michel Hersen. Oxford, Pergamon Press, 1988, 615 pp., $59.50; $24.50 (paper).

Women, Power, and Therapy, edited by Marjorie Braude. New York, Harrington Park Press, 1988, 340 pp., $14.95 (paper).

Freud and the Post-Freudians (1964), by J.A.C. Brown. New York, Penguin Books, 1988, 222 pp., $7.95 (paper).

Immaterial Facts: Freud's Discovery of Psychic Reality and Klein's Development of His Work, by Robert Caper, M.D. Northvale, N.J., Jason Aronson, 1988, 255 pp., $25.00.

Mutative Metaphors in Psychotherapy: The Aeolian Mode, by Murray Cox and Alice Theilgaard. New York, Tavistock and Methuen, 1987, 276 pp., $18.95 (paper).

A Remarkable Medicine Has Been Overlooked (1981, 1982), by Jack Dreyfus. New York, Dreyfus Medical Foundation, 1988, 168 pp., no price listed.

Rational-Emotive Therapy With Alcoholics and Substance Abusers, by Albert Ellis, John F. McInerney, Raymond DiGiuseppe, and Raymond J. Yeager. Oxford, Pergamon Press, 1988, 154 pp., $22.50; $12.95 (paper).

Psychology, Ethics and Change, edited by Susan Fairbairn and Gavin Fairbairn. New York, Routledge & Kegan Paul and Methuen, 1987, 271 pp., $45.00.

Planethood: The Key to *Your* Survival and Prosperity, by Benjamin B. Ferencz in cooperation with Ken Keyes, Jr. Coos Bay, Ore., Vision Books, 1988, 188 pp., $2.50 (paper).

American Psychiatric Press Review of Psychiatry, vol. 7, edited by Allen J. Frances, M.D., and Robert E. Hales, M.D. Washington, D.C., American Psychiatric Press, 1988, 673 pp., $49.95.

Preventing CAN Deaths: An International Study of Deaths Due to Child Abuse and Neglect, by Cyril Greenland. New York, Tavistock and Methuen, 1987, 205 pp., $77.50.

The Betrayal of the Self: The Fear of Autonomy in Men and Women, by Arno Gruen; translated from the German by Hildegarde and Hunter Hannum. New York, Grove Press (Random House, distributor), 1988, 149 pp., $16.95.

Psychology and the Critical Revolution, by Anton G. Hardy. Guilderland, N.Y., James Publications, 1988, 145 pp., no price listed.

The Key to Genius, by D. Jablow Hershman and Julian Lieb, M.D. Buffalo, N.Y., Prometheus Books, 1988, 220 pp., $19.95.

When Smart People Fail (1987), by Carole Hyatt and Linda Gottlieb. New York, Penguin Books, 1988, 240 pp., $7.95 (paper).

Interviewing the Sexually Abused Child, by David P.H. Jones and Mary G. McQuiston. London, Gaskell (Royal College of Psychiatrists), 1988, 56 pp., £4.50 (pamphlet).

Memory Disorders in Clinical Practice, by Narinder Kapur. Stoneham, Mass., Butterworths, 1988, 268 pp., $49.95.

Self-Conflict and Self Healing, by John King-Farlow and Sean O'Connell. Lanham, Md., University Press of America, 1988, 252 pp., $28.50, $14.25 (paper).

Patterns of Improvement in Depressed In-Patients: Institute of Psychiatry Maudsley Monograph 30, by Malcolm Lader, D.Sc., Ph.D., M.D., F.R.C.Psych., D.P.M., Reuben A. Lang, B.A., M.Sc., Ph.D., and Glenn D. Wilson, M.A., Ph.D., F.B.P.S. New York, Oxford University Press, 1987, 116 pp., $29.95.

Ethical Issues in the Psychotherapies, by Martin Lakin. New York, Oxford University Press, 1988, 164 pp., $24.95.

Enhancing Children's Social Skills: Assessment and Training, by Johnny L. Matson and Thomas H. Ollendick. Oxford, Pergamon Press, 1988, 99 pp., $22.50; $12.95 (paper).

Makers of Psychology: The Personal Factor, by Harvey Mindess. New York, Insight Books (Human Sciences Press), 1988, 176 pp., $26.95; $14.95 (paper).

Biological Contributions to Crime Causation, edited by Terrie E. Moffitt and Sarnoff A. Mednick. Dordrecht, The Netherlands, Martinus Nijhoff Publishers in cooperation with NATO Scientific Affairs Division (Norwell, Mass., Kluwer Academic Publishers Group, distributor), 1988, 331 pp., $96.00.

Medical Ethics: A Guide for Health Professionals, edited by John F. Monagle, M.A., Ph.D., and David C. Thomasma, Ph.D. Rockville, Md., Aspen Publishers, 1988, 500 pp., $49.50.

The Family Crucible (1978), by Augustus Y. Napier, Ph.D., with Carl A. Whitaker, M.D. New York, Perennial Library (Harper & Row), 1988, 293 pp., $8.95 (paper).

The Exceptional Brain: Neuropsychology of Talent and Special Abilities, edited by Loraine K. Obler, Ph.D., and Deborah Fein, Ph.D. New York, Guilford Press, 1988, 512 pp., $39.50.

Dreams of Love and Fateful Encounters: The Power of Romantic Passion, by Ethel Spector Person. New York, W.W. Norton & Co., 1988, 376 pp., $18.95.

Narrative Knowing and the Human Sciences, by Donald E. Polkinghorne. Albany, State University of New York Press, 1988, 228 pp., $44.50; $14.95 (paper).

Professional Conduct and Legal Concerns in Mental Health Practice, by Joan Rinas, Ph.D., C.Psych., and Sheila Clyne-Jackson, Ph.D., C.Psych. Norwalk, Conn., Appleton & Lange, 1988, 230 pp., $29.95.

The Riddle of Freud: Jewish Influences on His Theory of Female Sexuality. New Library of Psychoanalysis 4, by Estelle Roith. New York, Tavistock and Methuen, 1987, 189 pp., $55.00; $16.95 (paper).

Royal Rebel: A Psychological Portrait of Crown Prince Rudolf of Austria-Hungary, by John T. Salvendy, M.D. Lanham, Md., University Press of America, 1988, 255 pp., $26.75; $14.25 (paper).

The Work of Mara Selvini Palazzoli, edited by Matteo Selvini; translated by Arnold J. Pomerans. Northvale, N.J., Jason Aronson, 1988, 430 pp., $45.00.

Freedom From the Self: Sufism, Meditation and Psychotherapy (1985), by Mohammad Shafii, M.D. New York, Human Sciences Press, 1988, 253 pp., $14.95 (paper).

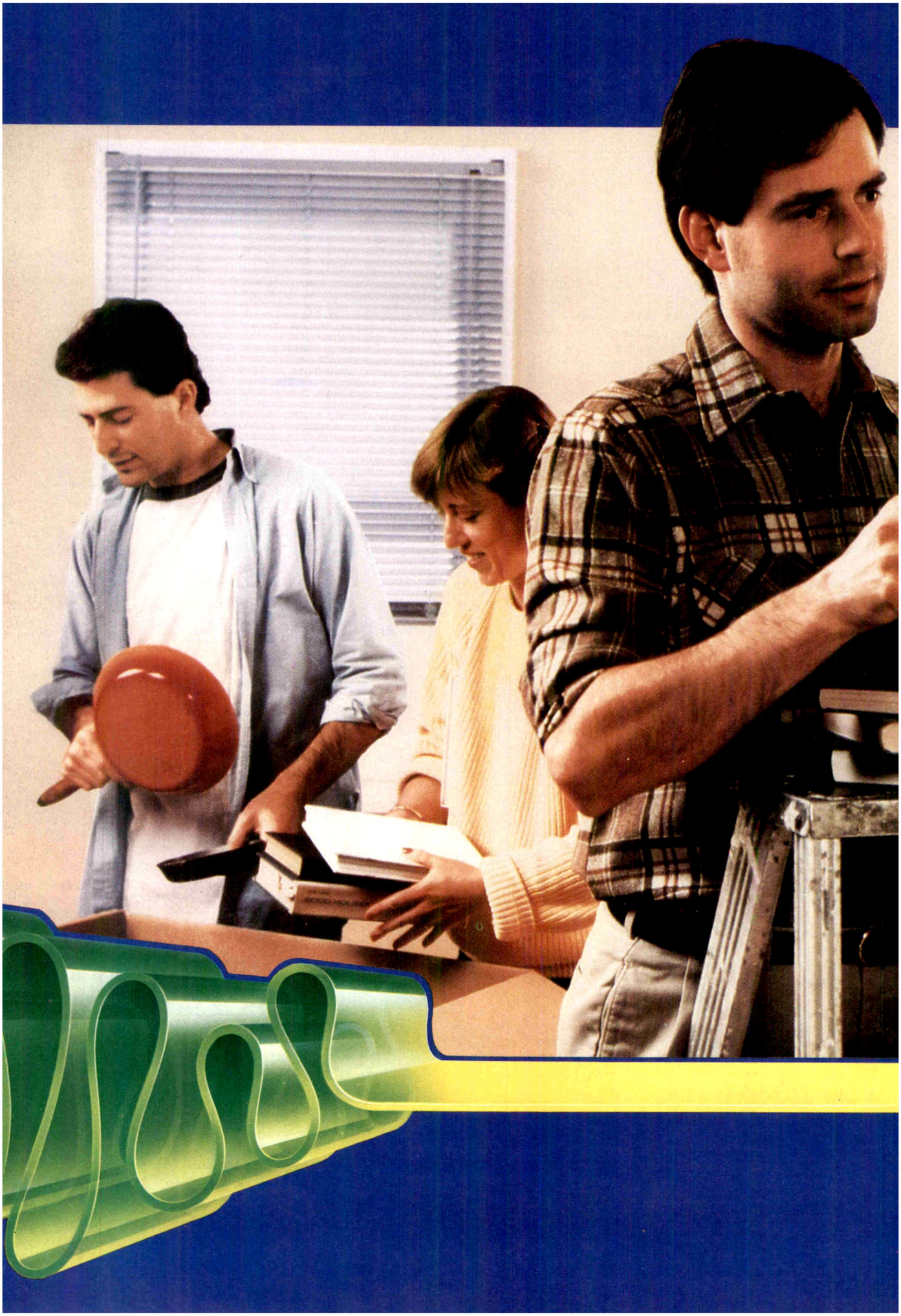
The Broad Range of Clinical Use of Phenytoin, Bioelectrical Modulator: Bibliography and Review, by Barry H. Smith, M.D., Ph.D., Samuel Bogoch, M.D., Ph.D., and Jack Dreyfus. New York, Dreyfus Medical Foundation, 1988, 246 pp., no price listed.

Epinephrine in the Central Nervous System, edited by Jon M. Stolk, David C. U'Prichard, and Kjell Fuxe. New York, Oxford University Press, 1988, 369 pp., $95.00.

The American Psychiatric Press Textbook of Psychiatry, edited by John A. Talbott, M.D., Robert E. Hales, M.D., and Stuart C. Yudofsky, M.D. Washington, D.C., American Psychiatric Press, 1988, 1,279 pp., $85.00.

The Physically and Sexually Abused Child: Evaluation and Treatment, by C. Eugene Walker, Barbara L. Bonner, and Keith L. Kaufman. Oxford, Pergamon Press, 1988, 204 pp., $23.50; $13.95 (paper).

Twenty-Fourth Report: WHO Technical Report Series Number 761, by the WHO Expert Committee on Drug Dependence. Geneva, World Health Organization, 1988, 34 pp., 6 Swiss francs (pamphlet).





For the schizophrenic patient

Sustained protection from relapse

About 60% of schizophrenic patients will experience relapse at some time.[1] Because of the increased risk of deterioration with each relapse, today's therapeutic challenge is to use all available measures to prevent its occurrence.[2] The sustained drug delivery of once-monthly HALDOL Decanoate Injection can be one factor in reducing the risk of relapse. Monthly administration assures that patients receive the prescribed dose of medication.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL® (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

References:

1. Johnson DA: Epidemiological evaluation of maintenance antipsychotic treatment, in Tognoni G, Bellantuono C, Laher H (eds): *Epidemiological Impact of Psychotropic Drugs*. Amsterdam, Elsevier/North Holland Biomedical Press, 1981, pp 205-220.
2. Lehmann HE, Cancro R: Schizophrenia: clinical features, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry*, ed 4. Baltimore, Williams & Wilkins, 1985, vol 1, pp 680-713.

Please see brief summary of Prescribing Information on next page.

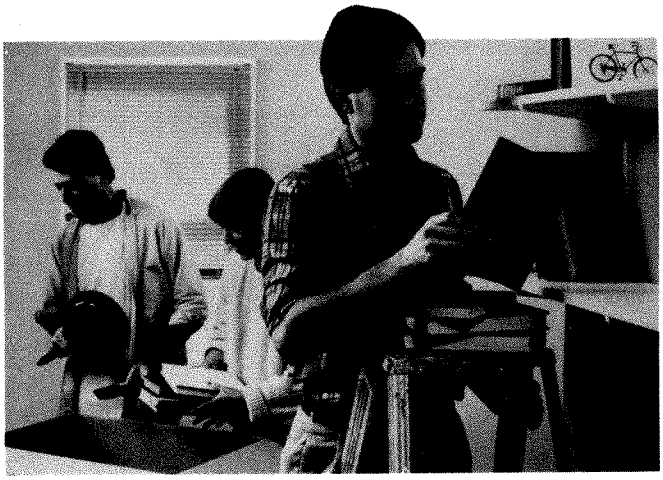
Once-monthly

HALDOL® DECANOATE (HALOPERIDOL) INJECTION

McNEIL PHARMACEUTICAL

McNEILAB, INC., Spring House, PA 19477

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HALDOL® DECANOATE
(HALOPERIDOL) INJECTION

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

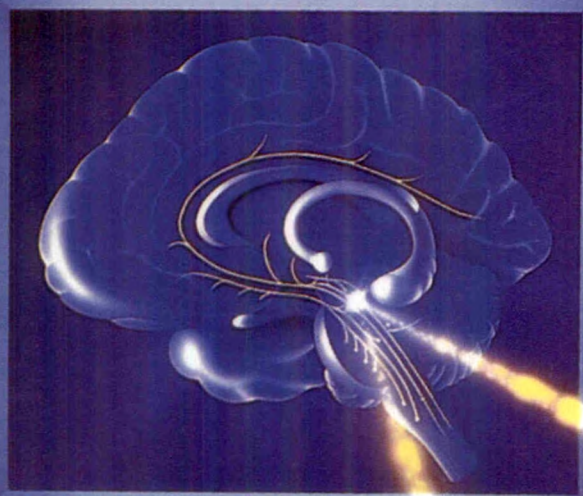
The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

6/3/87

For additional information, please call:
1-800-5-HALDOL (1-800-542-5365)

McNEIL PHARMACEUTICAL

McNEILAB, INC., Spring House, PA 19477



"There is considerable evidence that serotonergic function may be reduced in the brains of depressed patients."

Arch Gen Psychiatry 1984;41:398-402.



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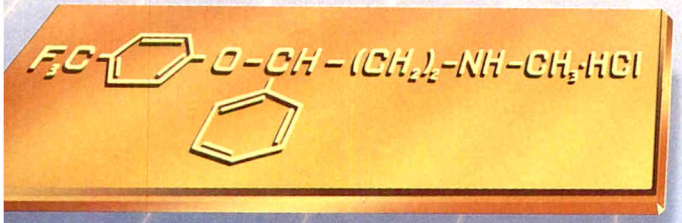
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PROZAC®

fluoxetine hydrochloride

A *specifically* different antidepressant

Chemically unrelated to all other available antidepressants.



Its distinctive chemistry means greater specificity.

The first highly specific...highly potent blocker of serotonin uptake

Effective treatment for depression

Fewer side effects to disrupt therapy

Side effects with Prozac® (fluoxetine hydrochloride) are generally mild and manageable and include nausea, anxiety/nervousness, insomnia, and drowsiness

Rash and/or urticaria occurred in 4% of clinical trial patients

Wide margin of safety

20-mg once-a-day therapy

Please see following page for brief summary of prescribing information.

DISTA

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Please send me complete product information on Prozac® (fluoxetine hydrochloride)

NAME _____ MD

ADDRESS _____

CITY _____

STATE _____ ZIP CODE

Return to: Dista Products Company
P.O. Box 5321
FDR Station

Prozac®
fluoxetine hydrochloride

Brief Summary. Consult the package insert for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindications: None known.

Warnings: *Rash and Accompanying Events*—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General*—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of Prozac-treated patients compared to 4% of placebo and 3% of tricyclic-antidepressant-treated patients. However, only rarely have Prozac patients been discontinued for weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Life of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. (*See* Clinical Pharmacology and Dosage and Administration sections)

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 753 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac.

- Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.
- Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.
- Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breast feeding an infant.
- Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monamine Oxidase Inhibitors—Although no clinical data are available on the effects of the combined use of fluoxetine and MAO inhibitors, it seems prudent to avoid their combined use until their potential for interaction has been studied systematically in controlled clinical trials. Based on experience with the combined administration of MAOI and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Prozac.

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients.

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children—Safety and effectiveness in children have not been studied.

Use in the Elderly—Prozac has not been systematically evaluated in older patients, however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Adverse Reactions: *Commonly Observed*—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials—The table that follows enumerates adverse events that occurred at a frequency of 1% or more among Prozac patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE
INCIDENCE IN PLACEBO-CONTROLLED
CLINICAL TRIALS

Body System: Adverse Event*	Percentage of Patients Reporting Event: Prozac (N = 1,730)	Placebo (N = 799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido decreased	1.6	—
Light-headedness	1.6	—
Concentration decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	—
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	—
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	—
Frequent micturition	1.6	—
Urinary tract infection	1.2	—
Special Senses		
Vision disturbance	2.8	1.8

*Events reported by at least 1% of Prozac patients are included.
— Incidence less than 1%.

Other Events Observed During the Premarketing Evaluation of During clinical testing in the US, multiple doses of Prozac were tered to approximately 5,600 subjects. Untoward events associ this exposure were recorded by clinical investigators using de terminology of their own choosing. Consequently, it is not pc provide a meaningful estimate of the proportion of individuals exp adverse events without first grouping similar types of untoward e a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictiona nology has been used to classify reported adverse events. The fr presented, therefore, represent the proportion of the 5,60C exposed individuals who experienced an event of the type cited c one occasion while receiving Prozac. All reported events are except those already listed in tables, those COSTART terms so ger be uninformative, and those events where a drug cause was rer important to emphasize that although the events reported did oc treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories an ated in order of decreasing frequency using the following de frequent: adverse events are defined as those occurring on one occasions in at least 1/100 patients; infrequent: adverse events occurring in 1/100 to 1/1,000 patients; rare: events are those oc less than 1/1,000 patients.

Body as a Whole—*Frequent*: chills; *Infrequent*: chills and fever, edema, hangover effect, jaw pain, malaise, neck pain, neck rig pelvic pain; *Rare*: abdomen enlarged, cellulitis, hydrocephalus, mia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System—*Infrequent*: angina pectoris, arrhythr orrhage, hypertension, hypotension, migraine, postural hypotens cope, and tachycardia; *Rare*: AV block (first-degree), brac bundle-branch block, cerebral ischemia, myocardial infarct bophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—*Frequent*: increased appetite; *Infrequent*: stomatitis, dysphagia, eructation, esophagitis, gastritis, gingiviti tis, liver function tests abnormal, melena, stomatitis, and thir bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ul itis, fecal incontinence, hematemesis, hepatitis, hepatomegal chlorhydria, increased salivation, jaundice, liver tenderness ulceration, salivary gland enlargement, stomach ulcer, tongu oration, and tongue edema.

Endocrine System—*Infrequent*: hypothyroidism; *Rare*: goiter, a thyroidism.

Hemic and Lymphatic System—*Infrequent*: anemia and lympl athy; *Rare*: bleeding time increased, blood dyscrasia, leukoper phocytosis, petechia, purpura, sedimentation rate increased, an bocythemia.

Metabolic and Nutritional—*Frequent*: weight loss; *Infrequen* alized edema, hypoglycemia, peripheral edema, and weight ga dehydration, gout, hypercholesteremia, hyperglycemia, hype hypoglycemic reaction, hypokalemia, hyponatremia, and iron d anemia.

Musculoskeletal System—*Infrequent*: arthritis, bone pain, tenosynovitis, and twitching; *Rare*: bone necrosis, chondrody muscle hemorrhage, myositis, osteoporosis, pathological fract rheumatoid arthritis.

Nervous System—*Frequent*: abnormal dreams and agitatio *quent*: abnormal gait, acute brain syndrome, akathisia, amnesia ataxia, buccoglossal syndrome, CNS stimulation, convulsion, de depersonalization, emotional lability, euphoria, hallucinations, hyperkinesia, hypesthesia, incoordination, libido increased, ma tion, neuralgia, neuropathy, paranoid reaction, psychosis, and *Rare*: abnormal electroencephalogram, antisocial reaction, chro syndrome, circumoral paresthesia, CNS depression, coma, dy dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclc stagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System—*Frequent*: bronchitis, rhinitis, and yaw *quent*: asthma, epistaxis, hiccup, hyperventilation, and pneumon apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung alveolitis, and pleural effusion.

Skin and Appendages—*Infrequent*: acne, alopecia, contact de dry skin, herpes simplex, maculopapular rash, and urticari eczema, erythema multiforme, fungal dermatitis, herpes zoster, hi psoriasis, purpuric rash, pustular rash, seborrhea, skin discolorat hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—*Infrequent*: amblyopia, conjunctivitis, ear p pain, mydriasis, photophobia, and tinnitus; *Rare*: blepharitis, c corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, ir sis, strabismus, and taste loss.

Urogenital System—*Infrequent*: abnormal ejaculation, amer breast pain, cystitis, dysuria, fibrocystic breast, impotence, leu menopause, menorrhagia, ovarian disorder, urinary incontinence retention, urinary urgency, urination impaired, and vaginitis. *Rar* tion, albuminuria, breast enlargement, dyspareunia, epididymitis lactation, hematuria, hypomenorrhea, kidney calculus, metro orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pi thritis, urinary tract disorder, urolithiasis, uterine hemorrhage, spasm, and vaginal hemorrhage.

Overdosage: *Human Experience*—As of December 1987, there w deaths among approximately 38 reports of acute overdose with flu either alone or in combination with other drugs and/or alcohol. Or involved a combined overdose with approximately 1,800 mg of fl and an undetermined amount of maprotiline. Plasma concentra fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respec second death involved three drugs yielding plasma concentra follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codei mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine enced two grand mal seizures that remitted spontaneously without anticonvulsant treatment (*see* Management subsection). Th amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involvin fluoxetine doses. Other prominent symptoms of overdose include tion, restlessness, hypomania, and other signs of CNS excitation for the two deaths noted above, all other overdose cases recovered residua

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CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity. Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL. Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis. Patients receiving SYMMETREL who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness and motor coordination are important.

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently. Because SYMMETREL is not metabolized and is mainly excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of SYMMETREL should be reduced in patients with renal impairment and in individuals who are 65 years of age or older. The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system stimulants. No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems.

Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women. SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The adverse reactions reported most frequently (5–10%) are: nausea, dizziness (lightheadedness), and insomnia. Less frequently (1–5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, and constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension and headache. Infrequently (0.1–1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, fatigue, skin rash, vomiting, weakness, slurred speech and visual disturbance. Rarely (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis and oculogyric episodes.

OVERDOSAGE: There is no specific antidote. However, slowly administered intravenous physostigmine in 1 and 2 mg doses in an adult* at 1 to 2 hour intervals and 0.5 mg doses in a child† at 5 to 10 minute intervals up to a maximum of 2 mg/hour have been reported to be effective in the control of central nervous system toxicity caused by amantadine hydrochloride. For acute overdosing, general supportive measures should be employed along with immediate gastric lavage or induction of emesis. Fluids should be forced and, if necessary, given intravenously. Hemodialysis does not remove significant amounts of SYMMETREL; in patients with renal failure, a four hour hemodialysis removed 7 to 15 mg after a single 300 mg oral dose.‡ The pH of the urine has been reported to influence the excretion rate of SYMMETREL. Since the excretion rate of SYMMETREL increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase the elimination of the drug from the body. The blood pressure, pulse, respiration and temperature should be monitored. The patient should be observed for hyperactivity and convulsions; if required, sedation and anticonvulsant therapy should be administered. The patient should be observed for the possible development of arrhythmias and hypotension; if required, appropriate antiarrhythmic and antihypotensive therapy should be given. The blood electrolytes, urine pH and urinary output should be monitored. If there is no record of recent voiding, catheterization should be done. The possibility of multiple drug ingestion by the patient should be considered.

DOSAGE AND ADMINISTRATION: Dosage for Drug-induced Extrapyramidal Reactions:
Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

HOW SUPPLIED: SYMMETREL (amantadine hydrochloride) is available as capsules (each red, soft gelatin capsule contains 100 mg amantadine hydrochloride) in:

Bottles of 100	NDC 0056-0105-70
Bottles of 500	NDC 0056-0105-85
Hospital Unit-Dose Blister Package of 100	NDC 0056-0105-75

As a syrup (each 5 ml [1 teaspoonful] contains 50 mg amantadine hydrochloride) in:

16 oz. (480 ml) bottles	NDC 0056-0205-16

Store at controlled room temperature (59°–86°F, 15°–30°C).

Capsules manufactured by R.P. Scherer-North America, St. Petersburg, Florida 33702 and Banner Gelatin Products Corp., Chatsworth, California 91311, for Du Pont Pharmaceuticals.

References:

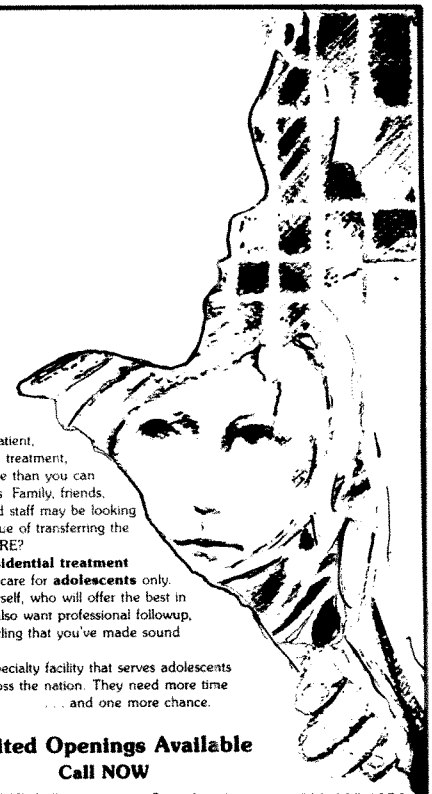
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* D.F. Casey, *N. Engl. J. Med.* 298:516, 1978.
† C.D. Berkowitz, *J. Pediatr.* 95:144, 1979.
‡ V.W. Horadam, et. al., *Ann. Intern. Med.* 94:454, 1981.

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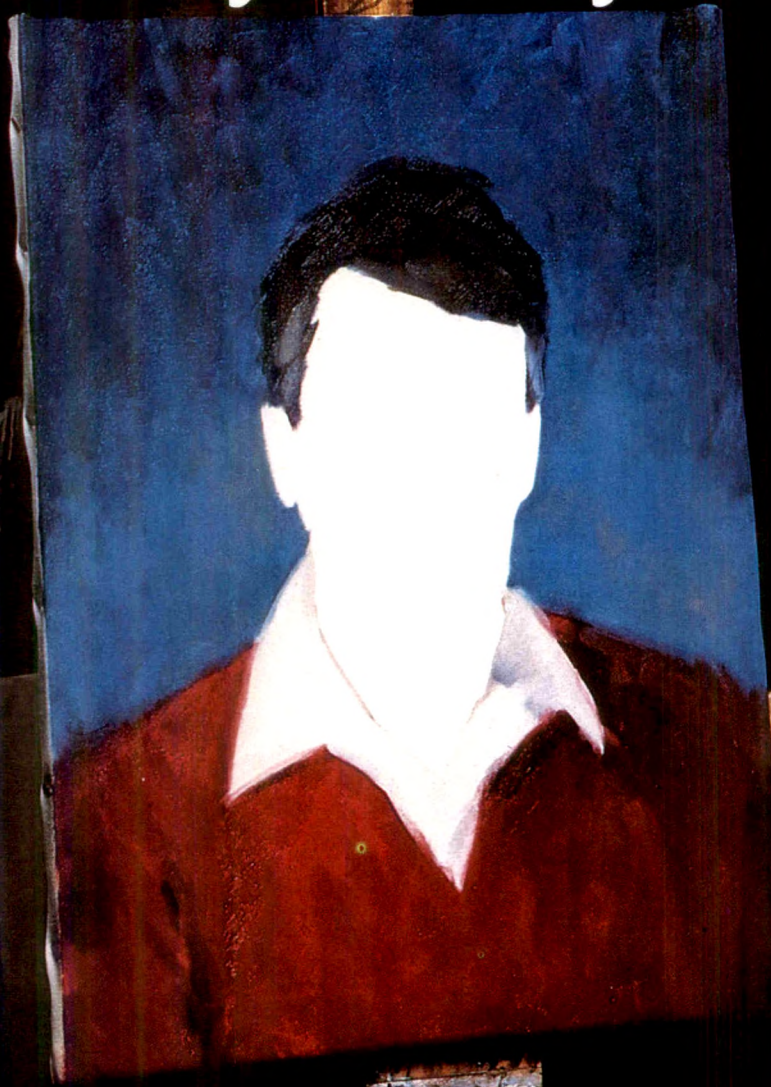
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Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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CONTACT:

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(202) 682-6091

Calendar

(Continued from page A11)

Davis, Executive Director, P.O. Box 708, Kent, OH 44240; 216-678-1601.

September 29, national conference, National Institute of Crisis Intervention Therapy and Research, Ainley Top, Huddersfield. Contact Dr. N. Rao Punukollu, Director, NICITR, 63 Nabcroft Ln., Crosland Moor, Huddersfield, HD4 5DU, United Kingdom; 0484-658054.

OCTOBER

October 3–6, annual meeting, American Academy of Family Physicians, New Orleans. Contact Robert Graham, M.D., Executive Vice-President, 1740 West 92nd St., Kansas City, MO 64114; 816-333-9700.

October 4, annual meeting, Black Psychiatrists of America, Trinidad. Contact Richard A. Fields, M.D., President, P.O. Box 370659, Decatur, GA 30037; 404-243-2110.

October 4–7, Second World Conference on Viruses, Immunity, and Mental Health, Montreal. Contact Prof. Dr. Edouard Kurstak, Dept. of Microbiology and Immunology, Faculty of Medicine, University of Montreal, C.P. 6128, Station A, Montreal, P.Q., Canada H3C 3J7; 514-343-6285; Telex 05267389; Telefax 343-6120.

October 5–8, annual meeting, Southern Psychiatric Association, Colorado Springs, Colo. Contact Margo S. Adams, Executive Secretary, P.O. Box 10002, Tallahassee, FL 32302; 904-222-8404.

October 5–12, annual meeting, International Federation for Medical Psychotherapy, Lausanne, Switzerland. Contact Finn Magnussen, M.D., President, P.O. Box 26, Vinderen, Oslo 3, Norway; 02-146190.

October 6–7, First International Conference on Refractory Depression, Philadelphia. Contact Jay Amsterdam, M.D., Depression Research Unit, Hospital of the University of Pennsylvania, 36th & Spruce Sts., Philadelphia, PA 19104-4283.

October 6–8, annual meeting, National Association for Retarded Citizens, Albuquerque, N.M. Contact Alan Abeson, Ed.D., Executive Director, 2501 Avenue J, Arlington, TX 76006; 817-640-0204.

October 6–9, annual meeting, Canadian Association for Community Living, Regina, Saskatchewan, Canada. Contact Diane Richler, Executive Vice-President, 4700 Keele St., Downsview, Ontario, Canada M3J 1P3; 416-661-9611.

October 6–9, Sixth Biennial International Symposium on Corpus Cavernosum Revascularization and Third Biennial World Meeting on Impotence, Boston. Contact Dept. of CME, Boston University School of Medicine, 80 E. Concord St., Boston, MA 02118; 617-638-4605.

October 7–10, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, Boston. Contact John A. Hinckley, Executive Director, P.O. Box 11083, Richmond, VA 23230; 804-355-0147.

October 9–11, national meeting, Mexican Association of Child Psychiatry, Queretaro City, Mexico. Contact Arturo Mendoza, M.D., Vice President, MACP, Patricio Sanz 437, Mexico, D.F. 03100; 905-523-1400.

October 9–15, XIV International Congress of Psychotherapy, Lausanne, Switzerland. Contact President, Prof. M. Burner, Centre Psycho Social, Rue St–Pierre 1, 1003 Lausanne, Switzerland; 021-44-21-33.

October 13–15, international conference, The Psychobiology of Human Eating Disorders, The New York Academy of Sciences, New York. Contact Conference Dept., The New York Academy of Sciences, 2 East 63rd St., New York, NY 10021; 212-838-0230.

October 13–15, 9th annual conference, Canadian Group Psychotherapy Association, Toronto. Contact Dr. Kent Mahoney, Holy Cross Hospital, 2210 – 2nd St., West, Calgary, Alberta, Canada T2S 1S6.

October 13–16, regional symposium, World Psychiatric Association, Washington, D.C. Contact Ms. Ellen Mercer, Director, Office of International Affairs, APA, 1400 K St., N.W., Washington, DC 20005; 202-682-6286.

October 14–16, biennial meeting, 6th International Conference on Psychonephrology, Chicago. Contact Norman B. Levy, M.D., Director, Liaison Psychiatry Division, Westchester County Medical Center, Valhalla, NY 10595; 914-285-8424.

October 15–20, annual meeting, American Academy of Pediatrics, San Francisco. Contact James E. Strain, M.D., Executive Director, P.O. Box 927, Elk Grove Village, IL 60009-0927; 312-288-5005.

October 16–18, part II examinations, American Board of Psychiatry and Neurology, Chicago. Contact Stephen C. Scheiber, M.D., Executive Secretary, ABPN, 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015; 312-945-7900.

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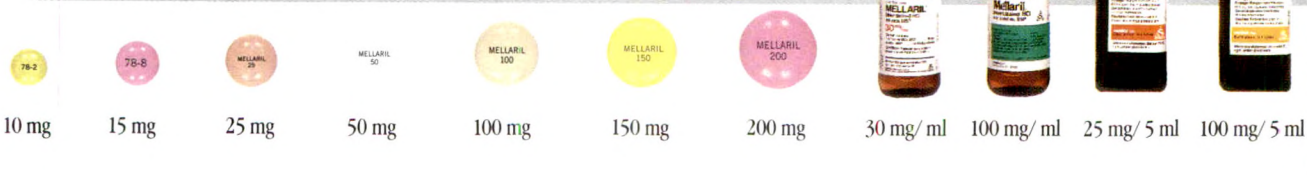
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Calendar

(Continued from page A20)

September 17, International Symposium on Sleep Disorders, Sao Paulo, Brazil. Contact Rubens Reimao, M.D., Rue Glicineas 128, 04048 Sao Paulo, SP, Brazil.

September 21–23, II Panamerican Sleep Congress, Buenos Aires. Contact Enrique Soltanik, M.D., Jufre 171, (1414) Buenos Aires, Argentina.

September 22, interim meeting, American Board of Medical Specialties, Chicago. Contact Donald G. Langsley, M.D., Executive Vice-President, One American Plaza, Suite 805, Evanston, IL 60201; 312-491-9091.

September 23–25, child psychiatry examination, American Board of Psychiatry and Neurology, Washington, D.C. Contact Stephen C. Scheiber, M.D., Executive Secretary, ABPN, 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015; 312-945-7900.

September 23–26, annual meeting, Royal College of Physicians and Surgeons of Canada, Ottawa. Contact Dr. J.H. Darragh, Executive Director, 74 Stanley Ave., Ottawa, Ontario, Canada K1M 1P4; 613-746-8177.

September 25–28, annual meeting, Alcohol and Drug Problems Association of North America, Inc., Charlotte, N.C. Contact Karst J. Besteman, Executive Director, 444 N. Capitol St., N.W., Suite 181, Washington, DC 20001; 202-737-4340.

September 25–28, annual meeting, Association of Mental Health Administrators, St. Louis. Contact Laurie Poul, Director, 840 North Lake Shore Dr., Suite 1103W, Chicago, IL 60611; 312-943-2751.

September 26–29, annual meeting, American College of Emergency Physicians, New Orleans. Contact Collin C. Rorrie, Jr., Ph.D., Executive Director, P.O. Box 619911, Dallas, TX 75261-9911; 214-550-0911.

September 26–29, annual meeting, World Medical Association, Vienna. Contact Angel Orozco, Executive Director, 28, Avenue des Alpes, 01210 Ferney-Voltaire, France; 50-40-75-75.

September 28–30, annual meeting, Canadian Psychiatric Association, Halifax, Nova Scotia, Canada. Contact Lea C. Metivier, Chief Administrative Officer, 294 Albert St., Suite 204, Ottawa, Ontario, Canada K1P 6E6; 613-235-2815.

September 28–October 1, annual meeting, American School Health Association, Lake Buena Vista, Fla. Contact Dana A. Davis, Executive Director, P.O. Box 708, Kent, OH 44240; 216-678-1601.

OCTOBER

October 3–6, annual meeting, American Academy of Family Physicians, New Orleans. Contact Robert Graham, M.D., Executive Vice-President, 1740 West 92nd St., Kansas City, MO 64114; 816-333-9700.

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October 5–8, annual meeting, Southern Psychiatric Association, Colorado Springs, Colo. Contact Margo S. Adams, Executive Secretary, P.O. Box 10002, Tallahassee, FL 32302; 904-222-8404.

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Psychological Medicine

Volume 18 Number 2 May 1988

EDITORIALS

Primary care as the middle ground for psychiatric epidemiology M. SHEPHERD & G. WILKINSON 263

Expressed emotion: current status I.R.H. FALLOON 269

Defining hysterical symptoms E. MILLER 275

HARE E. Schizophrenia before 1800? The case of the Revd George Trosse 279

GARATTINI S. & SAMANIN R. Biochemical hypotheses on antidepressant drugs: a guide for clinicians or a toy for pharmacologists? 287

ASHTON H., GOLDING J.F., MARSH V.R., THOMPSON J.W., HASSANYEH F. & TYRER S.P. Cortical evoked potentials and clinical rating scales as measures of depressive illness 305

CHRISTIE J.E., KEAN D.M., DOUGLAS R.H.B., ENGLEMAN H.M., CLAIR D. ST. & BLACKBURN I.M. Magnetic resonance imaging in pre-senile dementia of the Alzheimer-type, multi-infarct dementia and Korsakoff's syndrome 319

OWEN M.J., LEWIS S.W. & MURRAY R.M. Obstetric complications and schizophrenia: a computed tomographic study 331

LEWIS S.W., REVELEY M.A., DAVID A.S. & RON M.A. Agenesis of the corpus callosum and schizophrenia: a case report 341

DOLAN R.J., MITCHELL J. & WAKELING A. Structural brain changes in patients with anorexia nervosa 349

LOGSDAIL S.J., CALLANAN M.M. & RON M.A. Psychiatric morbidity in patients with clinically isolated lesions of the type seen in multiple sclerosis: a clinical and MRI study 355

GOLOMBOK S., MOODLEY P. & LADER M. Cognitive impairment in long-term benzodiazepine users 365

JAHANSHAHI M. & MARSDEN C.D. Personality in torticollis: a controlled study 375

ALDER E. & BANCROFT J. The relationship between breast feeding persistence, sexuality and mood in postpartum women 389

JACKSON P.R. Personal networks, support mobilization and unemployment 397

PLATT S., HAWTON K., KREITMAN N., FAGG J. & FOSTER J. Recent clinical and epidemiological trends in parasuicide in Edinburgh and Oxford: a tale of two cities 405

MAGAZINER J. Living density and psychopathology: a reexamination of the negative model 419

MAVREAS V.G. & BEBBINGTON P.E. Greeks, British Cypriots and Londoners: a comparison of morbidity 433

BRUGHA T.S., WING J.K., BREWIN C.R., MACCARTHY B., MANGEN S., LESAGE A. & MUMFORD J. The problems of people in long-term psychiatric day care. An introduction to the Camberwell High Contact Survey 443

BREWIN C.R., WING J.K., MANGEN S.P., BRUGHA T.S., MACCARTHY B. & LESAGE A. Needs for care among the long-term mentally ill: a report from the Camberwell High Contact Survey 457

WILLIAMS P. & SKUSE D. Depressive thoughts in general practice attenders 469

LEWIS S.N.C. & COOPER C.L. The transition to parenthood in dual-earner couples 477

HARRINGTON R., HILL J., RUTTER M., JOHN K., FUDGE H., ZOCCOLILLO M. & WEISSMAN M. The assessment of lifetime psychopathology: a comparison of two interviewing styles 487

DODWELL D. Comparison of self-ratings with informant-ratings of pre-morbid personality on two personality rating scales 495

SHARP D.J. Validation of the 30-item General Health Questionnaire in early pregnancy 503

BOOK REVIEWS

Philosophy and the Brain M.S. DE MOWBRAY 509

Work, Unemployment and Mental Health K.R. PARKES 511

Pain Management. A Handbook of Psychological Treatment Approaches R. JENKINS 513

The Experience of Illness J. MURRAY 514

Nine-Year-Olds Grow Up M.E.J. WADSWORTH 516

SHORT REVIEWS 518

PSYCHIATRY IN THE 1880s 521

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2. Glick ID, Hargreaves WA, Drues J, et al: Short versus long hospitalization, a prospective controlled study, VII: two year follow-up results for nonschizophrenics. Arch Gen Psychiatry 1977; 34:314–320
3. Rubinow DR, Post RM, Pickar D, et al: Relationship between urinary-free cortisol and CSF opiate binding activity in depressed patients and normal volunteers. Psychiatry Research (in press)
4. McNamara JR (ed): Behavioral Approaches to Medicine. New York, Plenum Press, 1979
5. Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in Endorphins in Mental Health Research. Edited by Usdin E, Bunney WE Jr, Kline NS. New York, Oxford University Press, 1979
6. Smythe GA, Compton PJ, Lazarus L: Serotoninergic control of human growth hormone secretion: the actions of L-dopa and 2-bromo-α-ergocyptine. Excerpta Medica International Congress Series 1976; 381:222–235

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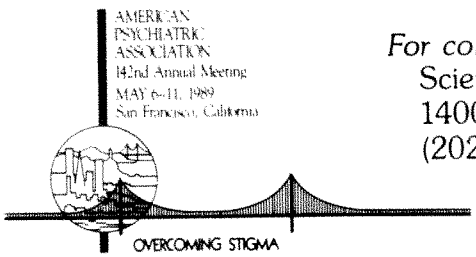
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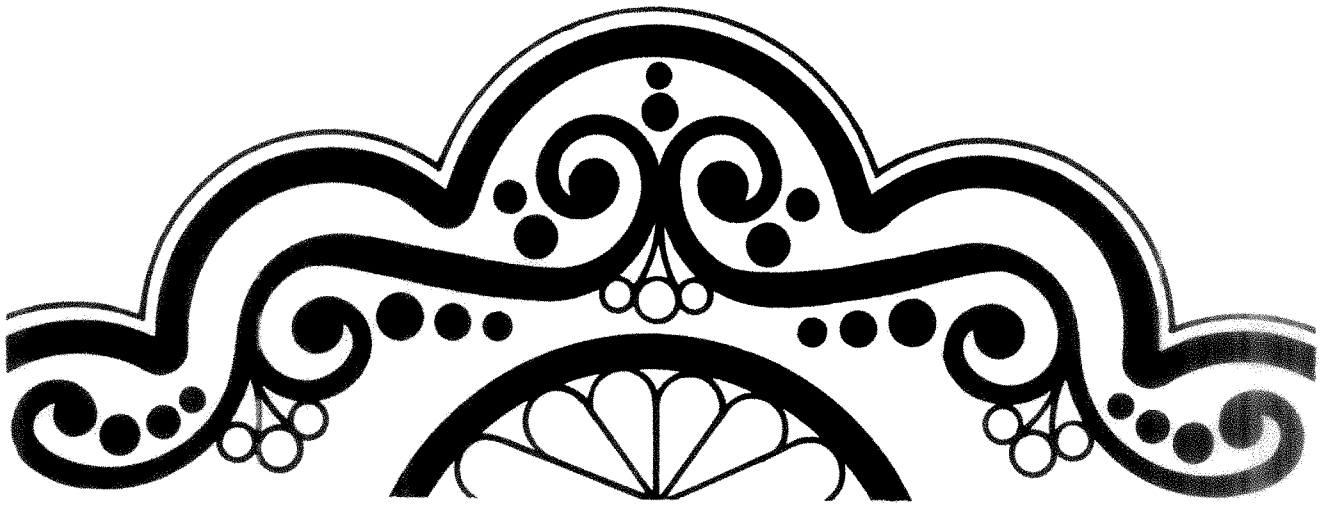
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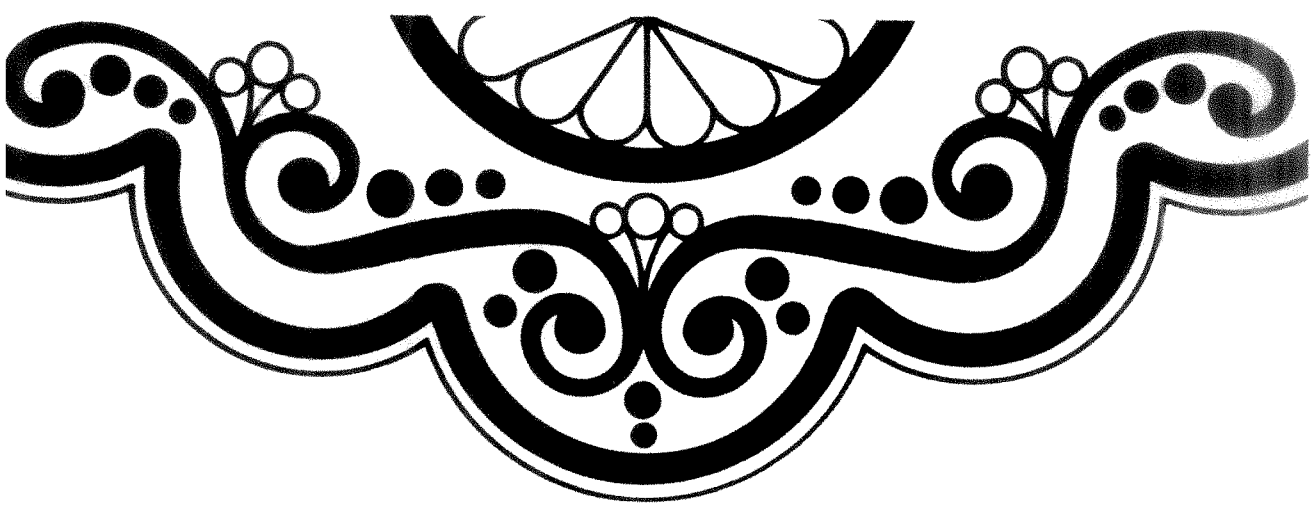
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THE AMERICAN JOURNAL OF PSYCHIATRY

The New Preventive Detention: Psychiatry's Problematic Responsibility for the Control of Violence

Paul S. Appelbaum, M.D.

The legal doctrine of the duty to protect potential victims of patients' violent acts has created problems beyond those usually discussed, which involve breach of patients' confidentiality. Fear of liability has led some psychiatrists to hospitalize, solely for the purpose of preventing violence, patients who do not otherwise require inpatient care. The result has been the creation of a de facto system of preventive detention that consumes psychiatric resources intended to serve therapeutic ends and compels psychiatrists to share the social control responsibilities of the criminal justice system. The author explores the costs and benefits of various means of removing the burden of preventive detention from psychiatry.

(Am J Psychiatry 1988; 145:779–785)

One of the most problematic judicial initiatives to affect mental health practice in the last decade has been the creation of the duty to protect potential victims of patients' violent acts. First elaborated in the California Supreme Court decision in *Tarasoff v. Regents of the University of California* (1), the doctrine has since been accepted in one form or another in more than a score of states (2). Even in jurisdictions where the doctrine has not yet been adopted by judicial decision—or more recently by statute—the duty to protect has become a reality of modern-day practice (3).

Mental health professionals have not been reticent in voicing their concerns about the problems created by court decisions regarding the duty to protect. From the first, they objected that the court-imposed requirements were likely to be futile—since clinicians lacked the ability to predict dangerousness and effectively to prevent it—and even deleterious—since patients' fears that their confidentiality might be breached would keep them away from needed therapy (4–6). It has been difficult to assess the validity of these concerns empirically, but they have continued to dominate the discussion of the future of the duty to protect.

It may be that one of the more important problems associated with the duty to protect lies not in breach of confidentiality but elsewhere: concern about potential liability is leading some clinicians to participate in the creation of a system of preventive detention for persons thought likely to commit violent acts. That is, these clinicians are hospitalizing persons who may or may not be mentally ill solely for the purpose of preventing them from engaging in violent behavior. Although some commentators anticipated that the duty to protect might increase pressure on clinicians to commit patients (5), the nontherapeutic turn this pressure would take and the effects it would have on psychiatric care were never fully appreciated. In this paper I will examine the influence of liability concerns on preventive detention in psychiatric facilities, explore the effects of psychiatric participation in preventive detention, and consider a range of possible responses.

PREVENTIVE DETENTION IN THEORY AND PRACTICE

Detaining persons to prevent future criminal behavior has a long and controversial history in both law and psychiatry in the United States. Dershowitz (7) noted that preventive detention (he used the term "preventive confinement") can occur in three circumstances: before the commission of any specifically pro-

Revised version of the 1986 Sam G. Dunn Lecture in Medicine and the Humanities delivered at the University of Texas Medical Branch in Galveston. Received Jan. 5, 1987; revised June 23, 1987; accepted July 27, 1987. From the Department of Psychiatry, Law and Psychiatry Program, University of Massachusetts Medical School. Address reprint requests to Dr. Appelbaum, Department of Psychiatry, University of Massachusetts Medical School, 55 Lake Ave. North, Worcester, MA 01605.

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scribed act, after the commission of a "dangerous" criminal act that in itself did not cause harm, and after the commission of a criminal act that has led to physical injury. One can in addition distinguish between detention that follows a finding of criminal guilt (with full procedural protections) and detention that is effectuated by some noncriminal mechanism and between detention that conforms with and detention that exceeds the usual limits of criminal confinement for similar acts. Detention before the commission of a criminal act, without a finding of criminal guilt, or in excess of the usual limits of criminal confinement are generally thought to be proscribed by the Constitution, since they seem to be unfair deprivations of liberty in violation of the requirements of substantive due process. Detention in mental health facilities solely for the purpose of preventing future violence may fall into all three of these generally proscribed categories.

Our society, however, has been ambivalent about preventive detention. At the same time that it has theoretically abjured such conduct, it has tolerated preventive detention on a practical level. Bail decisions in trial courts have long taken into account the likelihood that a prisoner will continue his or her criminal behavior while on bail, even though that practice has been considered constitutionally suspect. The federal Bail Reform Act of 1984, recently found constitutional by the U.S. Supreme Court (8), for the first time explicitly permits these considerations to enter into the bail decision. A previous decision of the Supreme Court (9) allowed preventive principles to be applied to pretrial release decisions concerning juveniles. And it has been an open secret that police departments have used misdemeanor statutes proscribing annoying behaviors such as loitering or creating a public nuisance to detain persons believed to pose the risk of more serious crimes.

It may be that preventive detention is in fact a necessary function in any society. Whatever their degree of dedication to civil liberties in the abstract, it is asking a great deal of people who believe that another person may soon act violently toward them not to take any measures to prevent that act from occurring. If our legal structure restricts the use of the criminal justice system for this purpose, then it might be argued that resort to the mental health system serves an affirmative social purpose.

Mental health professionals, however, have usually resisted seeing themselves as serving the purpose of preventive detention. When critics have charged that systems of involuntary commitment, particularly those which employ criteria based in part on dangerousness to others, are nothing more than mechanisms outside of the criminal process for protecting the safety of society (10), psychiatrists have disagreed strenuously. Psychiatrists point to treatment as the ultimate purpose of commitment, even if society—out of concern for limiting intrusions on autonomy—restricts the imposition of involuntary treatment to those who are dangerous to themselves or others. Unlike prisoners in a pure preventive detention system, patients committed to mental health facilities receive direct benefits from their detention beyond those society at large might derive.

This argument depends, however, on limiting involuntary commitment to those patients who are treatable in the setting to which they are being sent, actually providing the indicated treatment, and detaining them only long enough to accomplish the needed interventions. If any of these conditions are absent, the mental health system is in fact being used for preventive detention purposes. That is precisely what is happening today, as we encourage clinicians to assume responsibility for protecting victims of potentially violent persons in situations in which treatment is not possible. Court decisions following the *Tarasoff* precedent have suggested—as did *Tarasoff* itself—that when hospitalization is the only effective means of controlling a potentially violent person's behavior, clinicians may be expected to hospitalize the person. In fact, some decisions have limited the duty to circumstances in which commitment can take place (11). And psychiatrists have responded accordingly.

THE FACES OF THE NEW PREVENTIVE DETENTION

The most clear-cut examples of the new preventive detention in psychiatry are seen in the emergency rooms of psychiatric facilities, where potentially violent people are screened every day.

Case 1. A young man appeared at the emergency service of a large urban psychiatric hospital on a Saturday night, saying that he was afraid he would hurt someone. He had a long history of getting into fights and had recently served part of a several-year sentence in jail for assaulting his brother-in-law. He was now on parole. The man reported that he had been hitting his common-law wife and asked for help in controlling his temper. No symptoms of psychosis were present; a diagnosis of intermittent explosive disorder was made.

When the emergency room staff contacted the man's home catchment area, they were informed that a warrant had been issued for his arrest for the statutory rape of his daughter. The catchment area staff were unwilling to authorize his hospitalization, which was required for the admitting facility to be paid for his care. Despite the prospect of having to absorb the cost of hospitalization and substantial doubt about whether the patient had a disorder treatable in an acute hospital setting, the emergency room staff, with the concurrence of the hospital administration, decided to admit the patient to avoid the prospect of liability should he harm someone after being released.

The next morning the hospital was contacted by the patient's parole officer. Arrangements were made without the patient's knowledge to have him taken off the ward 2 days after admission and discharged into the custody of two police officers who would be waiting just beyond the unit's doors.

The psychiatrists and administrators involved in this case admitted the patient solely for the purpose of preventing the occurrence of violence, driven in large part by their fear of liability should they not detain the patient (12). No therapeutic considerations were present. As if to underline this point, the hospital staff secretly arranged transfer of the patient to the police not long after he was admitted. When the hospital received a threatening letter from the patient in jail several weeks later—charging that he had been betrayed by the hospital—the inpatient attending psychiatrist admitted that she was concerned about the role she and the hospital had played.

Psychiatry's preventive detention functions are not always so straightforward at the time of admission. Often patients will be admitted for valid therapeutic reasons but detained for preventive purposes beyond the point that any valid diagnostic or therapeutic benefit might be obtained.

Case 2. Several days after admission to a university medical center, a man in his late 20s was transferred to a state psychiatric hospital for assessment of his mental state. The man, who related a history of a seizure disorder, claimed he had suffered a "blackout" after taking an overdose of carbamazepine. Blood levels of the drug taken at the time of his admission, however, were in the normal range. Old hospital records showed that a previous neurological workup for seizures had been negative and that staff had concluded the patient was malingering to avoid outstanding charges of child molestation.

Evaluation at the state hospital revealed neither diagnosable psychiatric disorder nor evidence of suicidality; he refused to discuss his sexual deviance. After 2 weeks of psychiatric hospitalization, the psychiatrist in charge of this patient's care sought consultation concerning his disposition. The patient had been held for 2 weeks because his court date was scheduled for the following day and the hospital intended to discharge him directly to the court. Now, however, the patient was saying that he had no intention of keeping the date for his hearing. The psychiatrist expressed concern over releasing the patient because he feared he might be held in retrospect to have had an obligation to protect the public from subsequent acts of child molestation, the likelihood of which he was unable to assess.

Here, an arguably justifiable initial hospitalization was extended without therapeutic rationale to hold the patient before his court appearance. When even that seemed unlikely to effect continued confinement (or at least absolution of the psychiatrist from further responsibility), the psychiatrist asked—with genuine perplexity—just how long he would be expected to confine a potentially dangerous but uncooperative and, in this situation, untreatable patient in order to guarantee the public safety? The answer, given current judicial attitudes, is unclear. The psychiatrist in this case was aware that whenever the patient was released the occurrence of a violent sexual act would leave the psychiatrist open to potential suit for failure to protect the community.

Psychiatric responses to the uncertainty associated with this potential for liability sometimes include extreme measures aimed at lowering the risk. Yet, the intractability of chronic, characterologically based dangerousness often lends an air of desperation and futility to such efforts.

Case 3. I was contacted by a psychiatrist practicing in a distant state and asked if I would be available to consult on a case. Two months earlier, the psychiatrist had seen the patient in question, who was depressed over a physical injury and consequent loss of a well-paying job. The psychiatrist had prescribed medication. One week before the psychiatrist called me, the patient had been admitted voluntarily to a psychiatric hospital at the suggestion of his attorney. The patient had been threatening his brother and a used car dealer who he claimed had sold him a defective car; he had also beaten up his ex-wife.

On inpatient evaluation, the patient showed no signs of psychosis, although he was moderately depressed. He denied violent impulses. There was a clear history, however, of a lifetime of violent behavior, including abusing his ex-wife. He had beaten her severely when she testified against him in divorce proceedings. The patient came from a violent rural subculture in which hunters and fishermen who wandered unknowingly into his home area were often killed. To complicate matters, the patient had started to drink heavily and had recently joined a motorcycle gang.

The psychiatrist was calling to ask if I would fly in to consult on the patient. He had already obtained consultation from two local psychiatrists who had agreed that the patient was not psychotic or imminently dangerous in the sense that he intended to harm someone as soon as he was released from the hospital. The patient had already obtained maximum benefit from his hospitalization with regard to amelioration of his depression. The psychiatrist was concerned that at some point soon after release the patient would commit a violent act, which would result in the psychiatrist being sued. He sought consultation not so much for additional ideas for handling the patient as to provide documentation in court that he had left no stone unturned.

Regardless of the outcome of consultation, the psychiatrist intended to petition a court for the patient's commitment, although he believed hospitalization was no longer therapeutically required. He recognized, however, that this was only a partial solution to his dilemma. Even if a judge agreed to commit the patient, which he thought likely, he would still be left with the decision at some point as to when the patient should be released from the hospital.

The nub of the issue in this case from a clinical and policy perspective is that dangerousness and mental illness (as that term is commonly understood) are not synonymous. When the potential for violence is long-term and dissociated from any acute disorder that might exist, the current system provides powerful incentives for psychiatrists to prolong hospitalization beyond the term of useful treatment. Persons thought to be dangerous are deprived of freedom for a time but without therapeutic gain. Meanwhile, the long-term threat inevitably remains whenever the patient is discharged.

It should be emphasized that psychiatrists like the ones described in these case vignettes, although in some instances taking measures that may be thought

extreme, are not acting irrationally. They are responding in ways that might be considered counterproductive from the societal point of view relative to the use of scarce, expensive mental health resources. But the current incentives from the psychiatrists' perspective for such behavior are often too strong to be resisted. Psychiatrists are responding rationally by seeking to minimize liability, albeit at the cost of compromising their notions of what constitutes appropriate psychiatric care and transforming psychiatric facilities into de facto detention centers.

As difficult as the cases are in which patients have not yet committed a violent act that would permit their being turned over to the criminal justice system, the issues are still more complex when the police decline to accept responsibility for controlling persons whose behavior might legitimately put them within the purview of that system. Psychiatrists are then left to decide whether the scope of their responsibility to prevent violence exceeds that of the police and to struggle with how they might fulfill that obligation.

Case 4. A patient with chronic paranoid schizophrenia, alcoholism, and sociopathic traits often boasted to his therapist of having been involved in fights and having murdered people. His psychiatrist assumed the claims were generally untrue, although some months earlier the patient had beaten up his father. At his most recent session, the patient asked to be admitted to his catchment area hospital, but that facility refused on the grounds that hospitalization was unnecessary. When told this, the patient asked jokingly whether he needed to hit someone to get into the hospital.

Two days later, the patient returned and confessed that he had committed a murder in a downtown hotel with a transient population. He was referred to the police, who reported that his description of the victim and the scene of the crime was highly accurate. Nonetheless, the police told the psychiatrist that there were other ways in which the patient could have acquired the information, such as by hanging out in a bar with the real killer. They felt they lacked sufficient grounds to hold the patient. Their plan was to discharge him to the care of his mother and bring him in for questioning again the following day. Although the psychiatrist told the police that she believed the patient was potentially dangerous and may have committed the crime, her request that the patient be detained was rejected.

At that point, the psychiatrist sought consultation about her obligations to prevent further violence. Was she obligated (or even permitted) to commit the patient on grounds that the police found too flimsy to support criminal charges? If she failed to do so and violence occurred, would she be held liable, despite the man's release by the police (as was true in the original *Tarasoff* case)? What were the implications of her acting to hospitalize solely for preventive purposes?

This case involved a thoughtful and knowledgeable psychiatrist who became increasingly perplexed as the extent of her potential liability and the consequences of acting to avoid liability became apparent to her. Of particular concern was the recognition that her responsibility for protecting the public from a confessed murderer's further violence appeared to be greater than the police's responsibility. She resisted seeing herself as having a superior obligation in this regard but felt thrust into that role.

It should be noted—as demonstrated by the following example—that police may now be well aware of this dilemma and sometimes take advantage of psychiatry's potential utility as a mechanism for controlling persons who, for whatever reason, are still beyond the scope of the criminal justice system.

Case 5. A patient with diagnoses of antisocial personality disorder and alcohol abuse was being counseled in a drug and alcohol abuse treatment center located in an area of the city where a series of suspicious blazes had occurred. Knowing of the patient's past history of arson, always committed while he was drunk, the police questioned him and declared him their major suspect. However, they lacked sufficient evidence to charge him with the crimes. Instead, they asked the supervising psychiatrist of the drug and alcohol treatment center to place the patient on disulfiram to discourage him from becoming drunk, thus presumably snuffing out his fire-setting behavior.

The psychiatrist was concerned about the bind in which she found herself. There were clear clinical contraindications to beginning disulfiram in a patient of dubious reliability who now had alcohol in his blood. Even police pressure on the patient himself to ask for disulfiram, to which he ultimately bowed, did not change her opinion in this regard. But she was worried about the implications of failing to respond to a police request should the fires continue. The patient refused voluntary hospitalization for detoxification, which was the psychiatrist's treatment of choice, and could not be committed for alcoholism treatment.

The patient's parole officer became involved, asking the psychiatrist to work with him to get the patient to agree to voluntary admission. After several days of encouragement, the patient agreed to sign himself in. At that point, the parole officer had the patient's parole revoked on the grounds that admission for detoxification was evidence that he was drinking again, which violated his parole conditions.

The same dilemma that has led psychiatrists to participate in preventive detention of potentially violent persons has the potential to force them to extend their preventive functions outside the hospital setting. Although this psychiatrist resisted pressure to prescribe a medication she felt was contraindicated to assist the police in a situation in which they faced substantial public outrage over the continuing series of fires, not all clinicians might respond with such determination. Despite her efforts to avoid serving as an agent of public safety, however, she was ultimately unknowingly coopted by the criminal justice system. Her efforts to persuade the patient to admit himself to a detoxification facility—for his own benefit—served as the basis for revocation of the patient's parole and transfer to prison, where no further treatment was afforded. The criminal justice system in the end was successful in sharing with psychiatry its mandate to control violence.

EFFECTS OF PSYCHIATRIC PARTICIPATION IN PREVENTIVE DETENTION

The foregoing case examples document the ways in which clinicians feel compelled by the threat of liability to detain persons who would not otherwise be considered appropriate subjects for psychiatric hospitalization. Although extensive empirical data are not available on the extent of this behavior, my contact with mental health professionals around the country persuades me that similar effects of *Tarasoff* and its progeny occur widely. Data are in fact beginning to appear indicating the distorting influence that liability concerns can have on admission and release decisions (13). The surges in commitment reported in Washington State (14) and New York City (15) following widely publicized episodes of violence by mentally ill persons suggest similar phenomena. Assuming that the issue is common enough to warrant attention—while recognizing the need for additional data to establish the factual basis for that conclusion—we need to consider the benefits and costs associated with the practice of preventive detention in psychiatric facilities.

Without attempting to minimize them, I will put to one side concerns about civil liberties. They relate in large part to the fairness of detaining persons who have not yet been convicted of or, in some cases, not yet committed a crime. The debate over the legitimacy of preventive detention is an extensive and unresolved one that cannot be rehearsed here. Preventive detention is sufficiently unacceptable to many persons that they would look no further for a basis for absolving psychiatry of this task, although the U.S. Supreme Court has recently extended legitimacy to the concept (8, 9). Rather, I will focus on the more concrete effects of preventive detention in psychiatry.

On the positive side of the ledger, to the extent that dangerous people are being detained, society may gain some measure of safety. That was evidently the hope of the *Tarasoff* court when it justified its decision in these words: "In this risk-infested society we can hardly tolerate the further exposure to danger that would result from a concealed knowledge of the therapist that his patient was lethal" (1). If real, this is a benefit of importance to society. Further, it is a benefit that might be lost were the task turned over from psychiatry to the criminal justice system, since the latter is more closely constrained by constitutional concerns. Whether mental health professionals can accurately identify persons who are likely to commit violent acts, however, is a matter of hot controversy in the professions (16). It remains to be demonstrated that we are in fact detaining the right people. If our predictions are highly inaccurate and, as is likely, if people who come to psychiatric attention make only a minor contribution to the overall level of violence in our society, the benefits may be limited indeed.

The negative side of the ledger is crowded with more easily demonstrable factors. Persons who are unlikely to benefit from hospitalization are being admitted to our psychiatric facilities. They are consuming scarce resources, including money, space, and the attention of mental health professionals. At best, they gain nothing from this expensive endeavor and merely divert attention from patients in greater need of care. At worst, they actively disrupt the care of those patients, sometimes endangering them and the hospital staff. The staff are often ill-equipped to cope with violence that does not respond to standard psychiatric interventions. Morale is affected, as clinicians come to see themselves acting as policemen rather than pursuing therapeutic concerns. The staff, particularly the psychiatrists who are usually assumed to have ultimate legal responsibility for these patients, spend time and resources in often fruitless quests for security from lawsuits based on these persons' violence. Psychiatrists are confused about the relative weight of their clinical and legal obligations, and their decision making suffers as a result. Of course, the extent of these problems awaits confirmation in research studies, but anecdotal reports and clinical experience suggest they are not uncommon.

RESPONDING TO THE PRESSURES FOR PREVENTIVE DETENTION

If we assume some measure of agreement that the costs of using the psychiatric system for preventive detention outweigh the benefits, the question arises of how the burden of providing preventive detention should be removed from psychiatry. There are several possibilities, but—given that the duty to protect is itself not likely simply to go away and psychiatrists may in any event continue to feel an ethical obligation to prevent violence—it should be said at the outset that none of them is without problems of its own.

The least complicated approach would be for psychiatrists simply to disavow their availability to serve as agents of preventive detention. Ordinarily, plaintiffs must demonstrate that the standard of care has been breached to prevail in malpractice cases. Psychiatrists could refuse to admit persons who in their judgment do not require hospitalization for therapeutic purposes and could discharge those patients who have gained maximal benefit from their stay. If this became acknowledged as common practice in the profession, allegations that psychiatrists behaved negligently in failing to detain patients could be refuted with expert testimony that the standard of care in psychiatry does not countenance the use of mental health facilities solely for the protection of the public safety. Organized psychiatry might consider means of developing guidelines that could aid the evolution of standards of this sort.

For the sake of maintaining clinical integrity, I would favor this approach, but practitioners who adopt it must be forewarned that it involves certain risks. First, it represents a version of the well-known conundrum in which two prisoners are interrogated separately and each is promised a reduced sentence if

he or she implicates the other in a crime to which the police cannot otherwise link either. The maximal gain for each comes from silent solidarity; without a confession, they will both be released. But the fear that the other will yield first may lead each to break ranks and accuse the other, settling for a certain intermediate term rather than risking a more lengthy sentence.

In this case, psychiatrists who refuse to bow to legal pressure to use mental health resources solely to prevent violence are counting on their fellow clinicians to behave similarly in the hope that a solid front will persuade the courts that such action represents an acceptable standard of care. Those who give in to the understandable urge for self-protection, however, and hospitalize persons who are not likely to benefit therapeutically make this argument more difficult to sustain. When the latter group, in addition, act as expert witnesses at trials, testifying that nontherapeutic action to prevent violence is in keeping with psychiatric standards, the policy of simply disavowing responsibility for keeping the peace becomes more perilous still. The evidence presented in this paper suggests that clinicians, perhaps aware of this dilemma, have sometimes failed to resist the pressure for preventive detention.

An additional problem with this approach is that it may be insufficiently protective from a purely legal standpoint. *Tarasoff* itself (1), as well as other cases that have followed it (17), have rejected a professionally determined standard of care, holding psychotherapists to lay standards of reasonable behavior. The majority of courts that have issued opinions on the duty to protect have simply not addressed this question. It is difficult to know where the legal consensus will settle out.

A second approach to be considered involves more direct attempts to alter the legal rules governing the duty to protect. The alteration would specify that clinicians who refuse to detain persons not otherwise in need of hospital care are not liable for failing in the duty to protect. There are still problems, however, with this approach. It presumes that some consensus exists as to which patients do not require hospitalization. In all likelihood, expert testimony will be required on this point, and some clinicians would be willing to testify, as they do today, that hospitalization for the prevention of violence, particularly over the short-term, is an appropriate use of mental health facilities. They would argue that it both protects the public health and serves the interests of the person detained, since it is to no person's benefit to commit a violent act that may invoke punitive societal sanctions. Judges and juries, often interested in finding a basis on which to compensate victims, may well agree. Further, the frequently heard complaint that many dangerous persons should not be hospitalized because they are not mentally ill would be brushed off by these clinicians as a matter of semantics. Most dangerous persons can be given a *DSM-III* diagnosis, often of a character disorder, adjustment disorder, or intermittent explosive disorder. Courts have indicated that psychosis is not a requirement of the mental illness criteria of state commitment statutes (18). A similar conclusion would be likely here.

There might still be some value in restricting clinicians' liability for failure to hospitalize dangerous persons—as one court did recently (19)—since it would at least provide a solid basis for an affirmative defense in a trial. That value, however, is limited as long as psychiatrists continue to be responsible for protecting victims of the people they evaluate and treat, since hospitalization will often be the most effective means of fulfilling the duty. When the victims of violence cannot be located or identified in advance (and therefore cannot be warned), hospitalization may be the only effective intervention. Altering the rules of liability so as not to require hospitalization of dangerous persons is not likely to dissuade psychiatrists from resorting to detention as long as they continue to retain broad responsibility to protect potential victims.

Focal approaches to the problems caused by the new preventive detention are thus not likely to be successful. Rather, the misuse of mental health facilities inherent in psychiatry's fulfilling this role is one more factor contributing to the desirability of limiting liability related to the duty to protect in general. That process is underway in both legislatures and courts, often assisted by the support of organized psychiatry. Statutes in several states now restrict liability for failure to protect potential victims to situations in which clear threats have been offered against identifiable persons (20–29). The actions required of clinicians have also been limited; all of the statutes allow discharge of the duty to protect by informing the potential victim and/or the police. Only four specify involuntary hospitalization as a means of discharging the duty (21, 23, 27, 29), and even then alternatives are provided. It should be noted that, except for Washington State's statute (28), which provides for this explicitly, there is some question as to whether these statutes apply to situations in which inpatients are released and later commit violent acts (except for Washington's statute which provides for this explicitly [28]), since psychiatrists have traditionally been held to higher standards in these cases (Prof. Richard Bonnie, personal communication, September 1986). In addition, there may be some unfortunate clinical implications of encouraging clinicians to break confidentiality by warning potential victims as a first resort when violence is threatened (6). Nonetheless, these statutes have merit and clearly constitute a positive step toward limiting the pressure to engage in preventive detention.

The courts have also shown some willingness to limit the duty to protect in ways that may be helpful. These cases may serve to reassure psychiatrists that they will not always be found negligent, regardless of their behavior. In some cases, the courts have required that overt threats be made (30) or at least that victims be identifiable (31, 32). Since most *Tarasoff*-like cases are resolved before reaching the appellate level and are

therefore often unreported, it is difficult to know what percentage of cases are resolved in psychiatrists' favor on these or related bases. But clearly these too are positive developments. Unfortunately, in only a minority of jurisdictions have either legislative or judicial appellate decisions been made to restrict the extent of potential liability arising from the duty to protect.

People's desire to protect themselves from violence is understandable. Americans have been tempted since colonial times to preventively detain the mentally ill to achieve that end (7). Aside from questions about the legitimacy of preventive detention in general, the participation of mental health professionals in that process ironically might not have been nearly as problematic if they had been charged directly with this difficult task and not held responsible when inevitable failures occurred. Bringing preventive detention in through the back door by means of malpractice law, however, has led to a diversion of psychiatric resources from those with primary demands on them and has at times incapacitated clinicians who fear being sued for untoward consequences of their decisions. It would be better for psychiatry if it were relieved of the burden of preventive detention. It might be better for society as a whole for the question to be debated openly and, if provisions for some form of preventive detention are desired, for them to be implemented independently of the mental health system. The U.S. Supreme Court's recent acceptance of a structure for denying bail to persons facing serious criminal charges (under relatively strict procedures and after showings of proof of dangerousness have been made) (8) provides a possible model of such a system and should serve as a nidus for further debate.

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The *DSM-III-R* Personality Disorders: An Overview

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The revision of DSM-III *(*DSM-III-R*) includes substantial changes in the axis II personality disorders. The authors present and critically review these revisions and suggest directions for further research. The issues discussed include the multiaxial system, the use of a categorical rather than a dimensional format, the change from monothetic to polythetic criteria sets, the reduction in overlap among criteria sets, the decrease in the amount of unnecessary inferential clinical judgment required to make diagnoses, and the addition of two new personality disorders in an appendix. The criteria sets for many of the* DSM-III *personality disorders were also substantially revised in* DSM-III-R. *Changes in each of these are discussed in turn.*

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This paper provides an overview of the changes in axis II introduced by *DSM-III-R,* discusses their rationale, and indicates issues for future research and for *DSM-IV.* The revisions reflect a compromise with respect to issues about which the members of the Advisory Committee (appendix 1), as well as ourselves, were at times in disagreement. Space limitations prevent a complete discussion of each issue, but interested readers may consider the respective references for further discussion. The major general issues we consider are the multiaxial system, the use of a categorical model of classification, the change from monothetic to polythetic criteria sets, the reduction in item overlap, and the decrease in the degree of diagnostic inference. We also discuss the addition of self-defeating and sadistic personality disorders in an appendix to *DSM-III-R* and specific changes in the criteria sets of disorders retained from *DSM-III.*

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GENERAL ISSUES

Multiaxial Evaluation

Personality and developmental disorders are placed on a separate axis in *DSM-III-R,* consistent with *DSM-III,* to ensure that in the evaluation of adults these disorders are not overlooked when attention is directed to the usually more florid axis I disorder (1, 2). The *DSM-III* placement of the personality disorders on a separate axis may have also been instrumental in stimulating the considerable increase in personality disorder research (3, 4). This placement is to some extent arbitrary because any commonly overlooked disorder that is often comorbid with other clinical syndromes could be given a separate axis to ensure that it is considered. However, the developmental and personality disorders are relatively unique in that they generally begin in childhood or adolescence and persist in a stable form without periods of remission or exacerbation into adult life. Further attention, however, needs to be given to the validity, feasibility, and utility of additional axes (5, 6).

Categorical Classification

The Advisory Committee on Personality Disorders considered the inclusion of a dimensional classification of the personality disorders in an appendix to *DSM-III-R.* The boundaries between normal and abnormal personality styles and between the different personality disorders are to a large extent arbitrary (although latent class variables may underlie some of them) (3, 7–9). Many of the personality disorders may also lie along a spectrum of pathology (e.g., the avoidant along an anxiety, borderline along an affective, and schizotypal along a schizophrenic spectrum). However, it is not clear what the optimal set of dimensions to define the domain of personality disorder pathology would be (9–11). Persons could be rated in terms of the extent to which they displayed each of the 13 personality disorders presented in *DSM-III-R,* but this may be cumbersome and inefficient in clinical practice. Some of the disorders will be highly correlated, providing redundant information, and more fundamental dimensions may not be represented by any one of the current categories (12). One option is to include dimensions of affiliation (introversion-extraversion) and

power (dominance-submission) and basic clinical spectra (degree of affective dyscontrol, cognitive-perceptual aberrations, and anxiety). As yet, however, there are insufficient data to justify replacing the familiar and established diagnostic categories with an unfamiliar and unestablished dimensional system.

Polythetic Format

Notable progress was made by *DSM-III* in the development of explicit diagnostic criteria (13, 14). However, *DSM-III* was inconsistent in the way the criteria were used to diagnose personality disorders. Some criteria sets were monothetic, requiring all items to be present (e.g., schizoid, avoidant, dependent, and compulsive), while others were polythetic, containing a larger set of items and requiring the presence of only a specified number of them for diagnosis. Monothetic criteria sets are overly restrictive and incompatible with the heterogeneity of personality disorder symptoms (7, 15). Polythetic criteria improve reliability by not requiring agreement on the presence of every item in order to agree on the presence of the disorder. They also allow the inclusion of items that are not always present but are helpful in diagnosis (12). It was decided that in *DSM-III-R* each category would be polythetic. Each would consist of seven to ten items, and the presence of four to six would be required for diagnosis.

Questions remain regarding the use of the polythetic system. The number of items and cutoff points in the *DSM-III-R* criteria sets are inconsistent across diagnoses. An alternative approach would be to assume that each personality disorder diagnosis should entail an equal breadth of coverage, reflected in the use of the same number of items and cutoff points (as is proposed for *ICD-10*). However, an equal number of items and cutoff points may result in no more than the appearance of consistency, since the adequate definition of the boundaries of some disorders may require more items than others and some personality disorders may encompass a broader sphere of behavior than others.

Because most diagnoses are based on limited empirical data and the boundary between the presence and absence of a personality disorder is inherently arbitrary, the optimal cutoff points for establishing personality disorder diagnoses remain unclear (7, 8). Setting the threshold higher or lower can dramatically influence the base rates of given disorders and the overlap among them (16). Moreover, polythetic criteria sets may allow for more heterogeneity than is acceptable. For example, there are 93 different ways to meet the *DSM-III-R* borderline personality disorder criteria, and it is possible to meet the criteria without possessing unstable-intense relations, identity disturbance, or affective instability (17), even though most clinicians would agree that these are the hallmarks of the disorder. It appears that monothetic criteria sets are overly restrictive, resulting in too many false-negatives, but it is possible that adjustments to the cutoff points might improve the validity for some of the diagnoses (e.g., raising the criteria for borderline personality disorder from five to six of eight items, thereby reducing the frequency of false-positives). Whether borderline patients who possess only five of the relatively "minor" diagnostic criteria appear more like nonborderline patients than borderline patients should be assessed empirically.

Polythetic diagnosis of personality disorder might be improved further by weighting items in terms of their importance to the diagnosis; anchoring the criteria set to a single, necessary item (e.g., require social withdrawal in avoidant and schizoid criteria sets); recording the number of items possessed by each person to indicate whether the person represents a borderline, common, or prototypic case; and using flexible rather than fixed cutoff scores (12, 18). Weights, however, may vary dramatically across different settings (16), and flexible cutoff scores may interfere with communication across settings (19). In any case, empirical data on the effect of alternative cutoff scores and decision rules on large and diverse samples would be of considerable benefit to the developers of *DSM-IV*.

Overlapping and Multiple Diagnoses

There are many different systems for classifying personality traits and personality disorders, and the optimal representation and number of categories to partition the domain are unclear (4). The number of items in personality taxonomies has ranged from Hippocrates' four temperaments to Fourier's 810 character types (3). A low number tends to result in failure to represent clinically important personality descriptions, but increasing the number results in overlapping categories. The 13 personality disorders described in *DSM-III-R* are not the final word. The extensive degree of overlap may suggest an overrepresentation of some domains of personality disorder pathology and an underrepresentation of others. For example, some suggest that the proposed diagnosis of self-defeating personality disorder will provide little new information that is not already suggested by the diagnosis of dependent personality disorder (20), others suggest that the schizoid domain has been annexed by the avoidant and schizotypal (4, 21), and still others suggest that *DSM-III-R* fails to recognize the concept of a hypomanic personality disorder. Discriminant validity issues with respect to each personality disorder will be discussed later in this paper.

Overlap can also occur when the same or similar items are present in more than one diagnosis. There was considerable overlap among the *DSM-III* criteria sets (10, 11, 17, 22, 23), and this may provide redundant information, reduce reliability, and hinder the identification of specific etiologies and treatment. *DSM-III-R* attempts to decrease the overlap by deleting some of the overlapping items. Idealization/devaluation was deleted from narcissistic personality disorder and angry outbursts/tantrums was deleted from histrionic personality disorder primarily because they

were not central features but also because both items overlapped with borderline personality disorder. However, the deletion of overlapping items can at times be unnecessarily restrictive. Many of the personality disorders inherently correlate with one another and necessarily share characteristics, and it is therefore realistic to acknowledge this at the item level. For example, the avoidant, schizoid, and schizotypal personality disorders share the feature of social withdrawal. Deletion of this feature from one or two of them would have improved their differentiation, but the altered criteria sets would have misrepresented and distorted their description. In *DSM-III-R* the same item (having none to only one close friend or confidant) is included in all three criteria sets.

Clinical Judgments and Behavioral Specificity

It was noted in *DSM-III* that the diagnostic criteria referred to traits that are characteristic of recent (past year) and long-term (since adolescence or early adulthood) functioning, but specific temporal requirements were not given for any particular personality disorder except antisocial personality disorder (12). The diagnostic criteria are themselves to be considered examples or illustrations of the maladaptive traits described in the introductions preceding the criteria sets, and they are not infallible in their assessment of these traits. Although a goal of *DSM-III* was to reduce the level of inference required in judging criteria, this was especially difficult for the personality disorders (1), and there remained considerable room for disagreement in the assessment of individual items (24, 25). The criteria sets for *DSM-III-R* are designed, when feasible, to reduce further unnecessary subjectivity and inference. For example, the item "vain and demanding" was replaced by "overconcern with physical attractiveness" in histrionic personality disorder.

The optimal degree of behavioral specificity, however, is subject to controversy. Specific behaviors are only fallible indicators of a personality disposition because any single behavior can have multiple causes and represent multiple dispositions (12, 26). For example, accusing a husband of having an affair because he comes home late from work may suggest an unjustified concern with the spouse's fidelity (paranoid), suspicious or paranoid ideation (schizotypal), a demand for reassurance (histrionic), or a preoccupation with the fear of being abandoned (dependent). Vanity has many more behavioral representations than overconcern with physical appearance, and the assessment of this item is not itself without some problematic judgment (e.g., when does concern become overconcern?). Even acts judged to be prototypic examples of particular dispositions (22, 27) may not demonstrate adequate positive or negative predictive power (28). In addition, prototypic acts that exemplify particular personality dispositions and have high positive predictive power may occur too infrequently to be of much use in diagnosis, resulting in low negative predictive power. The *DSM-III-R* revisions were influenced heavily by research with semistructured interviews (23, 29–32), and some have suggested that this may at times result in too much emphasis on reliability and behavioral specificity. Reliability is necessary, but a narrow emphasis on reliability can result in the loss of constructs (traits) that are important or central to the understanding of a disorder (12, 33, 34). The extent to which clinical judgment is necessary to obtain valid clinical diagnoses will be an important area for future research.

NEW ADDITIONS TO *DSM-III-R*

None of the *DSM-III* personality disorders was deleted from *DSM-III-R*. Self-defeating and sadistic personality disorders are new additions to *DSM-III-R*, but their descriptions and diagnostic criteria appear not in the body of the text but in Appendix A, "Proposed Diagnostic Categories Needing Further Study."

Self-Defeating Personality Disorder

A masochistic personality disorder diagnosis was recommended for inclusion in *DSM-III* but not early enough to allow full consideration. The masochistic behavioral pattern also appears to be subsumed by the affective disorders (1, 34). Recommendations for masochistic personality disorder continued after the appearance of *DSM-III* (34–36; unpublished 1983 paper by R. Simons) and led to the 1985 proposed criteria for *DSM-III-R* (37).

The construct of masochism has had substantial clinical interest and precedent within psychology and psychiatry as well as psychoanalysis (38). A need for abasement was included in Murray's taxonomy of 20 basic human needs (39), and one of the eight interpersonal styles identified by Leary (40) was "self-effacing" that becomes "masochistic self-abasement" (p. 282) at a maladaptive level of expression. Schneider (41) included a description of a "depressive psychopath" in his taxonomy that is quite similar to masochistic personality disorder: "The basic common characteristic of depressives is the constant pessimism or at any rate their very skeptical view of life, which they seem to love in a rather dismal way. . . . Suffering is taken as a mark of quality and there is a tendency to establish an aristocracy of discomfort" (pp. 79–78). Sacco and Beck (42) described a negative, self-referential cognitive style characterized by a tendency to think of oneself as unworthy, incapable, and undesirable; to expect failure, rejection, and dissatisfaction; and to perceive most experiences as confirming these negative expectations. The psychoanalytic theories for masochistic personality disorder and the similar diagnosis of a depressive character have also broadened considerably beyond the early proposal of a confusion of pleasure and pain (unpublished 1983 paper of R. Simons; 38, 43–45).

However, the 1985 proposal for a diagnosis of masochistic personality disorder (37) generated remarkable controversy, and a meeting was held in November of 1985 to discuss it. The four major objections were that the diagnosis of masochistic personality disorder was biased against and/or harmful to women and victims of abuse (46, 47), that it was an affective rather than a personality disorder (48, 49), that it lacked empirical support, and that it was not sufficiently distinct from the dependent and passive-aggressive personality disorders (20). These critiques were helpful in developing the 1986 revised draft of *DSM-III-R* (50). Masochistic personality disorder was changed to self-defeating personality disorder to distinguish the diagnosis from the early psychoanalytic theory, and an exclusion criterion was added to ensure that the behaviors were not only in response to or in anticipation of being physically, sexually, or psychologically abused. The diagnosis of self-defeating personality disorder is intended for persons who repeatedly place themselves in abusive, detrimental, and injurious situations despite the opportunity to avoid them. An additional exclusion criterion addresses the overlap with depression. Self-defeating personality disorder must occur even when the person is not feeling depressed.

Empirical support for self-defeating personality disorder is limited, but it is equal to that available for most of the other personality disorders. Research by Kass et al. (44, 51) has indicated that the criteria set is internally consistent and can be reliably distinguished from other personality disorders. Additional research, however, is necessary to establish the disorder's construct validity and to assess empirically the purported costs of its potential misuse. Inclusion of the disorder in *DSM-III-R* will encourage the use of a uniform set of criteria in research and clinical practice. However, given the concerns regarding the potential for misuse and the lack of conclusive validity data, the diagnosis was not given official recognition in *DSM-III-R* as a personality disorder but remains in the status of proposed categories needing further study and was placed in the appropriate appendix. Clinicians can use the diagnosis, but it should be coded as a disorder of personality functioning that is not classifiable as a specific personality disorder (code number 301.90, personality disorder not otherwise specified), as one would diagnose other personality disorders that are not officially recognized (e.g., impulsive and immature personality disorders).

Sadistic Personality Disorder

DSM-III-R also includes sadistic personality disorder in the appendix of proposed diagnoses needing further study. Some critics charged (unfairly, we believe) that the purpose of including sadistic personality disorder was nothing more than to placate the critics of self-defeating personality disorder. There is substantial precedent, however, for the concept of a sadistic-aggressive personality style. Horney (52) provided a rich description of the "vindictive sadist," characterized by the repeated tendency to subjugate, dominate, disparage, deprecate, humiliate, berate, blame, defeat, and cruelly criticize others. These sadistic tendencies were not the result of sexual instincts but a bitter envy arising from repressed self-contempt and discontent. Fromm (53) described an "exploitative orientation" as abusive, manipulative, hostile, cynical, envious, and jealous. A precedent within psychiatry is Schneider's "explosive" psychopath, who is assaultive, short-tempered, abusive, and violent (41). Precedents within psychology include Leary's "aggressive-sadistic" interpersonal style (cold sternness, punitiveness, sadism, sarcasm, anger, irritability, criticalness, ruthlessness, provocation of guilt, and impatience) (40), Murray's "need for aggression" (39), and Millon's "aggressive" personality syndrome (temperamentally hostile, self-assertive, intimidating, unsentimental, self-reliant, malicious, explosively angry, domineering, humiliating, fearless, and antisocial) (54).

It remains to be documented, however, whether sadistic personality disorder is sufficiently distinct from antisocial personality disorder to warrant a separate category. Both are characterized by exploitation of others and are distinguished largely by the emphasis in sadistic personality disorder on aggressive and domineering rather than criminal behavior. Sadistic personality disorder is said to occur in persons without a childhood history of delinquent behavior and without an adult criminal history. However, it may be more parsimonious to simply note the presence of aggressive-sadistic tendencies in persons with antisocial personality disorder rather than to provide a new diagnosis.

REVISIONS OF CRITERIA SETS IN *DSM-III-R*

A number of criteria sets retained from *DSM-III* have been revised in *DSM-III-R*. To save space, we will not discuss in this paper any revisions that entailed only a minor refinement of an item.

Antisocial Personality Disorder

Antisocial personality disorder is one of the oldest, most established, and most heavily researched of the personality disorders and has been included in all previous versions of the *DSM*. The *DSM-III* and *DSM-III-R* formulations were based on extensive, systematic empirical research, particularly by Robins (55). Although *DSM-III* antisocial personality disorder had the most empirical support and highest interrater reliability, it was criticized for compromising validity for reliability by emphasizing easily identifiable criminal and delinquent behavior (1, 54, 56). The *DSM-III* criteria set may have selected too many criminals and excluded persons who were not criminal but who demonstrated the social irresponsibility, lack of guilt, disloyalty, lack of empathy, and exploitation central to

most theories of psychopathy (54). The *DSM-III-R* criteria set therefore added the psychological item "lacks remorse." Hare (57) has obtained reliable assessments of such constructs as lack of remorse or guilt, lack of sincerity, and glib and superficial charm. On the other hand, it has not yet been demonstrated that these ratings result in a different and more clinically useful diagnosis than that obtained by *DSM-III*. It will be necessary for future research to demonstrate that the inclusion of psychological constructs offers substantial incremental validity to the diagnosis.

Avoidant Personality Disorder

When it was introduced in *DSM-III*, avoidant personality disorder received considerable criticism for its deficient empirical support, lack of familiarity to clinicians, and close resemblance to the schizoid personality disorder (20, 35, 36, 58). Some (35, 36) suggested that it was only narrowly relevant to the taxonomy developed by Millon (54). However, avoidant personality disorder may actually have more utility than the schizoid diagnosis, as suggested by the fact that the prevalence rates in clinical settings for avoidant personality disorder are much higher than the rarely diagnosed schizoid personality disorder (10, 11, 21, 23, 30, 59). Many more persons appear to be socially withdrawn because of an anxious insecurity than because of an apathetic indifference. The *DSM-III* avoidant personality disorder criteria set, however, may have focused too heavily on social inhibition. *DSM-III-R* includes additional features of the psychoanalytic concept of the inhibited phobic character, such as an exaggeration of the risks in everyday life and an inordinate fear of being embarrassed (60). The nonspecific items "low self-esteem" and "desire for affection and acceptance" were deleted. An important focus for future research will be the comorbidity and overlap of avoidant personality disorder with anxiety disorders, particularly social phobia (4, 60).

Borderline Personality Disorder

It is not yet clear whether borderline personality disorder describes a distinct personality syndrome (8, 61–63), a subaffective disorder (64, 65), the overlap of affective and personality disorder pathology (60), a level of pathology (36, 54), or a heterogeneous hodgepodge. However, the decision to include borderline personality disorder in *DSM-III* was clearly useful, evidenced by the fact that it is currently the most heavily researched of the personality disorders (61). *DSM-III-R* revisions of this diagnosis are not substantial. The term "borderline" has been criticized for implying a reference to the overlapping boundaries between existing categories rather than to a distinct personality style. Nevertheless, the term was retained to maintain the association with the prevalent literature on borderline personality syndromes (1, 36, 61, 66). The item "intolerance of being alone" was deleted because it was shown to be inefficient in diagnosis (17, 23, 32) and overlapped with dependent personality disorder. The item "frantic efforts to avoid real or imagined abandonment" was added to represent more accurately the intense separation conflicts. Depersonalization/derealization and brief psychotic episodes, recommended by Gunderson (35, 61) for *DSM-III* and *DSM-III-R*, are still not included because there are conflicting data on the prevalence and discriminatory validity of these items (59).

Dependent Personality Disorder

Dependent personality disorder was included in *DSM-I* as a subtype of the passive-aggressive personality disorder, but it was not in *DSM-II*. Historical precedents include the psychoanalytic and psychological concepts of the oral and submissive characters, respectively. *DSM-III* dependent personality disorder was criticized for providing an excessively narrow definition (only three items) and for being biased against women (3, 67). The revision includes nine items that widen the construct by including submissiveness and fears of separation. The new items attempt to avoid the suggestion that they might apply to one sex more than another (e.g., the examples in *DSM-III* concerning the abdication of job decisions to one's spouse or the tolerance of an abusive spouse were revised or deleted). However, *DSM-III-R* may still be tapping dependency expressed through submissive behavior that is seen more often in women. It might have been useful to include stereotypically masculine forms of dependency expressed through domineering, assertive behavior (e.g., ordering others to help rather than begging or pleading) (60). It is debatable, however, whether equal prevalence across sex is desirable, since different rates may reflect different susceptibilities each sex has to particular personality disorders (68–70).

Histrionic Personality Disorder

DSM-III histrionic personality disorder was criticized for being closer to low-functioning, infantile, hysteroid dysphoria (65, 71) than to the classic psychoanalytic formulation of hysterical personality (36, 72). The revision of histrionic personality disorder deleted the items that overlapped with borderline personality disorder (manipulative suicidal behavior and angry outbursts and tantrums) and added the more classic feature "inappropriately sexually seductive in appearance or behavior" (72). Future research should continue to address the question of a possible sex bias in the diagnosis, whether alternative male and female items should be included (an item representing, for example, the macho male), and whether histrionic personality disorder and antisocial personality disorder refer to gender variants of the same underlying disorder (67, 68, 72–76).

Narcissistic Personality Disorder

Narcissistic personality disorder was a new addition to *DSM-III* that represented growing interest in the theoretical and clinical concept of narcissism (1, 36, 77). The *DSM-III* criteria set was criticized for its lack of empirical support (20, 35) and for not recognizing that narcissism appears in a variety of forms other than overt grandiosity, exhibitionism, and feelings of entitlement (72, 78, 79). Items tapping conflicts regarding envy (36) and the belief that one's problems are unique were added in *DSM-III-R*. Items deleted were the alternation between idealization and devaluation, since it overlapped with borderline personality disorder, and cool or indifferent response to criticism or indifference, since its prevalence was difficult to evaluate (23). It has been suggested that the diagnosis of narcissistic personality disorder can be made only in the context of a transferential relationship (72, 79, 80). However, this would limit the diagnosis to patients of very skilled clinicians using psychoanalytic psychotherapy. It is preferable to use items that represent easily recognized styles of interpersonal relatedness that are not limited to a particular type of psychotherapy.

Obsessive-Compulsive Personality Disorder

The obsessive-compulsive personality disorder was included in all previous versions of the *DSM* and has historical precedents in psychoanalysis (e.g., anal character), psychiatry (e.g., anankast character), and psychology (e.g., autocratic and conforming personality). The *DSM-III* formulation received few criticisms. Although it has been infrequently diagnosed in some studies sampling inpatient and outpatient clinics (10, 11, 23, 30), obsessive-compulsive personality disorder may be more prevalent in private practice. *DSM-III-R* expanded the criteria set to include items that better represent the original psychoanalytic constructs of parsimony and orderliness as well as obstinacy (81). The title was changed from "compulsive disorder" because "compulsive" was descriptively inaccurate, implying an emphasis on behaviors over cognitions. Many obsessive-compulsive patients are driven to think rather than to act. There was a suggestion to include a Type A personality disorder diagnosis in *DSM-III-R*, but this seemed premature and the behavior pattern may already be represented by obsessive-compulsive and narcissistic traits (82).

Paranoid Personality Disorder

Paranoid personality disorder was included in all previous versions of the *DSM* and has historical precedents primarily in the psychiatric literature (20). The 16 items used to diagnose paranoid personality disorder in *DSM-III* were reduced to seven in *DSM-III-R* to make it more manageable and consistent with the other criteria sets. The four items concerned with restricted affect were deleted because they overlapped with schizoid personality disorder and were better conceptualized as associated features rather than principal characteristics. Several items were combined into one item tapping suspiciousness. Nonspecific items were deleted (e.g., "inability to relax" and "exaggeration of difficulties"), and a new item was added, "bears grudges or is unforgiving of insults or slights." Future research should address the question of whether paranoid personality disorder belongs within a schizophrenic or a paranoid spectrum (4, 35, 83).

Passive-Aggressive Personality Disorder

Passive-aggressive personality disorder was included in the first *DSM*, reflecting the military psychiatric experience in World War II (54, 84). The *DSM-II* formulation included more emphasis on the psychoanalytic concept of the "oral-sadistic" character. Passive-aggressive personality disorder was almost excluded from *DSM-III* because it was considered by some to be a situational reaction to being a powerless subordinate (35, 84). It was finally included with the restrictive condition that it not be diagnosed in the presence of any other personality disorder. This exclusion criterion has usually been ignored in the research and was deleted from *DSM-III-R* so that this aspect of personality could be recognized despite its occurrence with other personality disorders. Nevertheless, when diagnosing passive-aggressive personality disorder it is particularly important to demonstrate that the behavior is evident in a variety of situations (12). The *DSM-III* criteria set for passive-aggressive personality disorder may have also defined too narrow a construct that focused only on the indirect resistance to external demands (54, 60, 68). The revised criteria set was broadened to include hostile negativism, resentment, unreasonable criticisms, and unjustifiable protestations.

Schizoid Personality Disorder

Schizoid personality disorder was included in all previous versions of the *DSM*. It was originally formulated within psychiatry on the basis of observations of the biological relatives and premorbid personalities of schizophrenic patients, a domain now subsumed by schizotypal personality disorder. Introverted schizoid styles have also been prominently recognized in the personality theories in psychology and the object relations theories in psychoanalysis. The *DSM-III* formulation was rarely diagnosed in clinical settings (10, 11, 23, 30, 59). The very low prevalence may result from the restrictive, monothetic criteria set for schizoid personality disorder (it is rare to find patients who one can confidently state have an absence of warm, tender feelings and are indifferent to praise, criticism, and the feelings of others). In addition, many patients who were previously diagnosed as having schizoid personality disorder may now be diagnosed as having avoidant personality disorder because most introverted persons are anxious and ambivalent (not apathetically

indifferent) or as having schizotypal personality disorder because apathetic or indifferent persons may also demonstrate eccentricities of speech, thought, and/or behavior (85). In *DSM-III-R* one can diagnose both schizoid and schizotypal personality disorders in the same patient because the schizoid personality disorder exclusion criterion of no schizotypal eccentricities has been deleted. However, this compromise may not make much sense because little new information may be provided by a schizoid personality disorder diagnosis in addition to the schizotypal diagnosis. Schizoid and schizotypal personality disorders may be but slightly different variants of a single personality disorder or different points along a schizophrenic spectrum (4, 85). The *DSM-III-R* criteria set for schizoid personality disorder was expanded from three to seven items. The new items provide further indicators of social indifference, blunted affect, and anhedonia. Schizoid personality disorder was retained because of its long clinical tradition and the lack of sufficient data to argue for its deletion, but it will remain to be seen if the expansion will increase the frequency or usefulness of the diagnosis.

Schizotypal Personality Disorder

The *DSM-III* items for schizotypal personality disorder were derived in part from efforts to characterize borderline schizophrenic individuals among the biological relatives of schizophrenic patients who displayed mild or attenuated schizophrenic symptoms (66). A number of studies have since indicated that the *DSM-III* schizotypal personality disorder criteria set may not be optimal in identifying these biological relatives, who are best characterized by social isolation, inadequate rapport, social dysfunction, suspicious interpersonal relationships, eccentric behavior, frequent somatic problems, and emotional coldness or detached affect (86, 87). It was therefore suggested that schizotypal personality disorder be revised to emphasize these social-interpersonal items (negative symptoms) and to deemphasize the cognitive-perceptual aberrations (positive symptoms). Although these proposed revisions might have been helpful in establishing a genetic link between schizotypal personality disorder and schizophrenia and would increase the distinction between schizotypal personality disorder and borderline personality disorder, the ability to identify biological relatives of schizophrenic patients should not be the major validating criterion for the diagnosis of schizotypal personality disorder (88). The subjects identified as schizotypal in the familial research may not be comparable to the schizotypal patients seen in clinical settings, they rarely present for treatment, and they may not demonstrate the level of dysfunction that would warrant psychiatric diagnosis and treatment. Studies within clinical populations have indicated that positive items are usually more efficient than negative items in diagnosing schizotypal personality disorder (23, 89–92; unpublished 1985 paper of T. McGlashan).

The *DSM-III* schizotypal personality disorder criteria set also closely resembles the definition for the prodromal and residual phases of schizophrenia, a similarity enhanced by the addition in *DSM-III-R* of the item "odd, eccentric, or peculiar behavior or appearance." It was suggested that the criteria set be identical to the prodromal/residual phases. If schizotypal personality disorder refers to a borderline schizophrenia and the criteria set is revised to equal these phases of schizophrenia, it seems reasonable to consider placing schizotypal personality disorder within a schizophrenic spectrum, along with the schizoid and schizophreniform disorders, rather than within the personality disorders section (1, 35, 93). This is being suggested for *ICD-10* and would be consistent with the *DSM-III-R* placement of the cyclothymic and dysthymic disorders (1, 34). However, schizotypal disorder may also be appropriately placed within axis II, even if it is considered a variant of schizophrenia, because it would refer to the characterologic manifestation of schizophrenic pathology (i.e., a mild but pervasive expression with a chronic, stable course without fluctuating episodes of psychosis or remission).

CONCLUSIONS

We hope that the *DSM-III-R* criteria sets will prove to be an improvement over *DSM-III*. They will and should generate further research and discussion. The optimal cutoff scores for the polythetic criteria sets, the degree of overlap, and the relative balance of clinical judgment and behavioral specificity need to be assessed empirically. Whether and how to replace or supplement the categorical diagnoses with assessment of severity of dimensions are unclear. Considerable empirical attention has been given to antisocial, borderline, and schizotypal personality disorders, but little research has been conducted on self-defeating, sadistic, avoidant, and narcissistic personality disorders, and much of the research concerning dependent, histrionic, obsessive-compulsive, paranoid, passive-aggressive, and schizoid personality disorders occurred before the appearance of *DSM-III*. There are several empirical questions concerning each personality disorder, beyond the basic issues of reliability, etiology, course, and treatment. Many of these were noted here in the discussion of each disorder.

Despite the many changes that have been made, inconsistencies in the diagnosis of personality disorders remain. There is variation in the breadth of coverage, evident in part by the variation across criteria sets in the cutoff points, number of items, and behavioral specificity. There is a lack of consistency in the emphasis on cognitive, affective, behavioral, and interpersonal features. Some of the criteria sets emphasize affective features (e.g., borderline), while others emphasize cognitive (e.g., paranoid), behavioral (e.g.,

antisocial), or interpersonal (e.g., dependent) features. In future systems it may be preferable for each disorder to include systematically each area of personality functioning (54). On the other hand, it must be recognized that some personality disorders may manifest themselves more in one area than another and that a systematic representation of each area may be unnecessary and distorting.

A final lack of consistency is international. The forthcoming *ICD-10,* scheduled to appear in 1992, will not contain the same set of personality disorders or criteria sets included in *DSM-III-R*. This diversity may be useful in that it allows contrasting viewpoints to be considered and does not force a premature closure of disagreements. However, it is also unfortunate because the inconsistencies are problematic to the communication of empirical and clinical findings (94). The *DSM* and the *ICD* are converging, but there should perhaps be a more systematic effort to improve congruency.

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APPENDIX 1. Members of the Advisory Committee on Personality Disorders

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Supervision and Privacy in Psychotherapy Training

R. William Betcher, Ph.D., M.D., and Norman E. Zinberg, M.D.

Supervision is an essential element of training in psychotherapy, and the issue of privacy in relation to the supervisory process is an important one. The authors examine the attitude toward privacy implicit in each of the two major models of supervision, the so-called didactic and countertransference models. They consider the ways in which supervision, particularly the countertransference model, and the use of audiovisual devices intrude on the privacy of the therapist and the therapy. Finally, they consider how the institutional and professional structures within which supervision takes place deal with the issue of privacy.

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Supervision is an essential element of training in psychotherapy. Vast numbers of papers and books have been written about it, and most training programs assiduously attempt to upgrade their supervisory efforts. However, important disagreements about the goals, process, and technique of supervision remain; these can be broadly categorized into two different models. One model of supervision seeks to instill in the trainee a body of knowledge about psychotherapy, including theory, principles, and technique; its mode of teaching is primarily didactic and rational, and its focus of study is primarily the patient. The second model is more personal and experiential; in this view, the trainee's most crucial learning occurs by attending to the countertransference as it becomes manifest in his or her reactions to the patient and is mirrored in the "parallel process" of supervision.

There has been little evaluation of the impact of either model of supervision on the process of psychotherapy or the development of the therapist who is being supervised. A reputation for "good" supervision is often what attracts trainees to a particular training program, and supervision is generally acknowledged to be the most useful, if not the only, way to learn to be a psychotherapist. At the same time, however, most therapists in training experience supervision as a personal intrusion, albeit a necessary one. Most of them report feeling a difference in the therapeutic situation once they have finished training and are "alone" with their patients. However, mental health professionals are so accustomed to using supervision as a teaching procedure that it is difficult for them to see it as impinging on trainees' privacy and therefore on their security within the training program.

The purpose of this article is to examine the issue of privacy in the supervisory process by addressing three questions. First, what attitude toward privacy is implicit in each of the two major models of supervision? Second (and this is by far the most complicated question), how does supervision—especially that which is oriented toward countertransference or the use of audiovisual devices—intrude on the privacy of both the therapist in training and the therapy? Third, how do the institutional and professional structures within which supervision takes place deal with the issue of privacy?

We will refer from time to time to two previous articles on privacy (1, 2) and will reiterate some of the key concepts presented in them. The first article differentiated the private from the public interview, defining the private interview as "one in which the therapist and the patient or the group of patients (which could include a family) are all participating in the experience without any form of external observation." The second article defined the most important elements in that privacy. The review of the literature given in those two articles showed that the importance of privacy has received less attention from psychiatrists than from sociologists, one of whom equated the cultural significance of the invention of the door with that of the acquisition of fire (3). There is little agreement in the psychiatric literature on the extent to which turning a private interview into a public one affects psychotherapy. It is widely believed that therapists resist direct observation of interviews more strongly than their patients do; one possible reason for this—interference with the therapist's ability to undo a mistake—was addressed in the second article.

ATTITUDES TOWARD PRIVACY IMPLICIT IN TWO MODELS OF SUPERVISION

To obtain a fresh perspective on the first question, concerning the two basic models of supervision and their implications for privacy, we held nine meetings

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with the supervising faculty of a large community mental health center that has more than 100 members and then conducted interviews with 15 senior supervisors to explore the issue of privacy in more depth. Considerable agreement was reached on a number of basic issues. The supervisors ostensibly eschewed rigidity and spoke of the necessity of modifying supervisory routine in accordance with three basic factors: the clinical situation; the problems of the patient; and the level of education, the experience, and the personality of the therapist being supervised. All of the supervisors regarded therapy as dynamically interactive and felt that supervision needed to address the unconscious as well as the conscious aspects of mental functioning, internal conflict, developmental sequences, and the relationship of the patient to the therapist in training. It was also agreed that therapists should be sensitive at all times to their own personal conflicts, values, attitudes, affects, and orientation in order to keep these from intruding on the therapy.

Differences of opinion emerged on certain questions. For example, should supervisors get to know their trainees personally? Should they discuss matters other than the therapy during the supervision? Should they be concerned with evaluating the therapists they supervise? Should they provide reading lists? Should supervisors feel direct responsibility for patients? Should patients know that the therapist is being supervised? Should the supervisor be willing to see, or even insist on seeing, the patient whose therapy is being supervised? Should tapes (usually audiotapes rather than videotapes) be used?

The sharpest division of opinion among the supervisors we interviewed appeared between those, on the one hand, who believed that the therapist's feelings and attitudes about and during the session were the principal focus of supervision and those, on the other hand, who thought that gaining an understanding of the patient and of a body of knowledge about therapy was most important. The first group tended to think of supervision as complex but very much like therapy, while the second group saw it as resembling other teaching situations. Supervisory techniques diverged, of course, along the same lines.

This split is reminiscent of the earliest days of organized training in psychoanalysis. Originally, the student therapist's personal analysis and work with patients were emphasized. Supervision by someone other than the therapist's analyst came later, followed by reading seminars and course work. Very early in the history of psychoanalysis, a debate developed between the Hungarian and Viennese schools of thought about psychoanalytic training. The Hungarian school stressed the importance of the control (or training) analysis and thought that the therapist's irrational feelings about the patient should be dealt with in the control analysis, which would effectively serve as supervision. The Psychoanalytic Institute of Vienna maintained that the student therapist's personal analyst should not supervise the student's first cases but that different points of view should be presented. Thus, in Vienna students were expected to work with someone who would teach and not analyze them, and any personal issues that emerged in this didactic exercise were referred to the student's own analyst.

In our nine meetings with supervisory faculty, differences of opinion over the same issue proved to be as sharp and rigid as they had been between the Viennese and Hungarian schools. "This is how I do it" was oddly synonymous with "This is the *right* way to do it." Most of the supervisors on both sides of the debate had not thought of supervision as an invasion of privacy, nor had they recognized that the two sides represented polarized approaches to the subtle issues of privacy. On the one hand, too much respect for the trainee's privacy, expressed as an emphasis on understanding the patient and/or a body of theory, may well miss the therapist's personal conflicts about a particular patient or a particular theoretical position. On the other hand, too great an emphasis on the therapist's personal feelings, i.e., the countertransference—particularly with the introduction of mechanical aids—may constitute an invasion of privacy. While both approaches, in the extreme, do not constitute good supervision, at this time it is the latter that appears to present the greater problem.

INTRUSION OF SUPERVISION ON THE PRIVACY OF THE THERAPIST AND THE THERAPY

In what ways, then (and this is the second and largest of our questions), does supervision—especially supervision based on countertransference and the use of audiovisual aids such as tape recorders—intrude on the privacy of the therapist and the therapy? In the second of the earlier articles we have mentioned (2), four elements were singled out that highlight the need for privacy in the development of a psychotherapeutic relationship: the rhythm set up by two people (therapist and patient), which establishes interacting boundaries and judgments; the level of concentration of one person upon the other; the capacity for undoing human error; and the nature of a relationship that studies itself. In supervision the same four elements play a part. The therapist-supervisor dyad also develops a rhythm, a tangibleness of boundaries and cognizance of judgment, and a capacity for interactive undoing of human error similar to these elements in therapy itself. Supervision, too, may become a relationship that studies itself if the supervisor is inclined toward the countertransference or "parallel process" model of supervision.

The Therapist's Viewpoint

In supervision the therapist trainees are expected to tell what has passed between them and their patients. In doing so they realize that their reporting reveals

their own personality structure, conflicts, and vulnerabilities. The degree to which the supervisor explores these areas will depend in part on his or her model of supervision. The supervisor who emphasizes the therapist's learning about himself or herself as a supervisory tool tends to probe more deeply. The therapist welcomes this attention up to a point; after all, it is a part of the learning process. But every therapist in supervision wonders just how much of the hidden self is being exposed to this other person whose keen powers of observation are buttressed by greater experience. Further, because the trainee's presentation is intended to be about the patient's therapy rather than the trainee, the trainee is deprived of the defenses that might be present in his or her own therapy.

In any regular, ongoing therapy, the patient has the opportunity to tell his or her story in such a way that the nuances of the tale protect areas of greatest sensitivity. Patients are also protected by knowing that they are in the spotlight. In any supervision, however, there is an ambiguity about whose development is of basic concern. On the one hand, supervised therapists have someone looking over their shoulder at their therapy and are therefore never really alone with their patients; on the other hand, they are not really alone with their supervisors, because the patients in effect decide much of what will be discussed in both places. This lack of a clear center around which to present oneself can lead to greater defensiveness in supervision than in therapy itself. Especially in a countertransference-oriented supervision, or when there are no clear limits set on exploration of the therapist's personal life, therapists are apt to feel exposed and, further, to feel that they will be evaluated adversely if they are not receptive to such intrusions.

Therapist trainees' anxiety about this invasion of privacy is ameliorated by their basic desire to learn and also by their ability to modify to a certain extent what they present. Interchanges with the patient may be forgotten, modified, or placed in different contexts. In part, this is a function of the nature of the material—like dreams, the therapy process quickly escapes recall—but it is also a function of the therapist's defensiveness. Much of this goes on outside the therapist's awareness and may or may not become apparent to the supervisor. For example, one supervisor, after listening to a therapist's process notes, wondered aloud why the patient seemed to be talking about people who had left her. At this point the therapist remembered that he had announced he was going on vacation, but he had "forgotten" to record this in the process notes. Not infrequently, distortion of process notes is conscious and may even be deliberate: one therapist, whose supervisor was rigidly psychoanalytic and criticized him for saying anything at all to his patients, decided to bracket his comments in his written notes so that when he read them aloud to the supervisor, he could edit out most of his own statements.

The Supervisor's Viewpoint

Thus far we have considered privacy from the therapist's vantage point. What about the supervisor? Ekstein and Wallerstein (4) observed that before therapists become supervisors, they have had considerable therapeutic experience. Thus, they know more about therapy than supervision, are more secure about their skills as therapists than as supervisors, and have ample reason to see supervision as similar to the situation they know better. Imperceptibly, this could lead to considering trainees as patients and concentrating on their personal aberrations and idiosyncrasies, including labeling these inaccurately as countertransference. The degree to which this model of supervision has become ingrained is seen in Ekstein and Wallerstein's book, which has been widely regarded as an authoritative source. In spite of their warnings about such reductionism in supervision, these authors constantly emphasize the personalities and emotional difficulties of the trainees they describe.

The literature on observed psychotherapy (5–12) has consistently reported that therapists tend to be more concerned than patients about the invasion of privacy. As for therapists who are supervisors, it is paradoxical in a logical sense, but understandable from a psychodynamic viewpoint, that because they themselves are afraid of exposure, they defensively press for maximal exposure of their trainees. Lewis's work on the phenomenology of shame and guilt (13, 14) provides some insight into this paradox. Lewis suggests that patients' embarrassment is inevitably evoked in therapy and that therapists reporting to their supervisors undergo a similar threat of shame about being seen as incompetent. Moreover, we suggest that to the extent that supervisors are not able to acknowledge their own vulnerability, they will tend to take a polarized position in the classic dialectic between the personal and the didactic—either turning supervision into a limitless and possibly shame-inducing exploration of the trainee's personal frailties or, at the opposite pole, insisting that any personal conflict inadvertently revealed by the trainee be dealt with outside the supervisory relationship.

Supervisors who do not wish to pry too far into the personal responses of their students have other problems, some of which also have implications for the privacy of the student. Given the inherent ambiguity of therapy and its reliance for effectiveness on the therapist-patient relationship, a supervisor whose approach is too didactic may easily remain unaware of personal conflicts in the trainee about a particular patient or about therapy in general. Although it is generally true that the best "cure" for countertransference problems is a clear understanding of the patient, therapists (and particularly inexperienced therapists) do find their work emotionally arousing. In a comfortable supervisory situation, such experiences can be discussed without fear of either therapylike, limitless exploration or cursory dismissal that remands those concerns to the

student's own therapist, if he or she has one. This is an extremely fine line to walk—one that most experienced supervisors know very well. Finding that line is, in itself, a deeply personal matter which may expose the shyness, aggressiveness, or righteousness of the supervisor. This subtle concern about personal exposure may well explain both the rigidity of the supervisors in the faculty meetings we described earlier and the lack of published material about privacy and supervision.

Effects of Supervisors' Interviews With Patients and Use of Audiovisual Devices

Other privacy issues exist for the group of supervisors who like to interview a trainee's patients themselves or who rely on recordings of interviews. Such supervisors may be tempted to encroach on the therapist's privacy because it is difficult to get an accurate picture of what is going on in the therapy; this situation can be frustrating, especially if the supervisor is inexperienced or thinks that the patient is in real trouble. Fears about accuracy can sometimes lead to methods that further intrude on the therapist's personal domain and on the therapy. Few supervisors approve of the therapist's taking copious process notes during the interview with the patient. However, having rejected that option, some supervisors feel that they either must see the patient themselves (with or without the therapist present) or must hear a recording of a session. Sometimes the supervisor's meeting with the patient or reviewing a tape clears up points that have been hard to explicate; this can set a therapy back on course and can eventually provide a common frame of reference for supervisor and trainee.

These procedures also carry a price, however. They may interfere with the natural rhythms and boundaries of the "private" (i.e., the less closely monitored) therapy situation, since the process of supervision may be seen, like the process of therapy presented in the second of the earlier articles (2), as having a rhythm of its own. As in a dance, the supervisor takes the lead by providing an independent sense of what is going on with the patient. Then he or she waits, ready to follow the rhythm of therapy, to see how this information is integrated by both therapist and patient.

This subtle interplay can be disrupted if the therapist feels more self-conscious when the supervisor "knows too much." For example, if the supervisor has seen the patient, the therapist presenting a view of the patient from the therapy material knows that the supervisor may have a different view, based not entirely on the interactions presented but on the supervisor's reactions to his or her own interview with the patient. That concern may force the therapist into either greater doubt about what is going on in the therapy or greater intransigence if the therapist thinks the supervisor's views rest on issues that are no longer relevant. In the case of a tape, the therapist's concern about exposure may result in similar interference with the supervisory process.

In theory, therapists in training should attempt to tell supervisors as fully as possible what is going on in the therapy. In fact, therapists often have opinions and ideas of their own about what works well but are reluctant to disagree openly with their supervisors. For example, a 4th-year psychiatric resident presented the case of a young man, Mr. A, who had felt "dumped" by a girl. Both supervisor and therapist recognized that although the patient had ruminated at length about the rejection, he had not shown any anger. The supervisor suggested that the patient's wish to please others was so great that he perceived himself as a manipulator who had not deserved the relationship in the first place. The resident saw the sense in this formulation but still wondered about the absence of anger. For several sessions the resident and the supervisor discussed other patients and then they moved back to Mr. A. At that point the resident "confessed" that he had postponed presenting the case of Mr. A again because, after the earlier discussion, he had pressed the patient to reveal angry feelings instead of following the course suggested by the supervisor. "It felt as if the anger had to be there, so I went after it. To tell you the truth, I hadn't believed the extent to which giving people what they want was a part of him. It is just as you predicted. Now, every week I get anger. I didn't want to tell you because I thought you would disapprove." This "mistake" led not only to a more precise understanding of the patient but eventually to a useful theoretical discussion about abreaction versus the delineation of character structure. In the views of both the resident and the supervisor, it led to a more fruitful teaching situation.

The forging of an individual style of therapy may at times require resistance to supervision and at other times willingness to take in new information and points of view. If Mr. A's therapy had been observed or taped, more might have been learned, but the sequence that occurs in supervision after concealment or resistance would not have been the same. In particular, the working through of differences between supervisor and trainee might not have occurred. In the second of the earlier articles on privacy (2), the point was made that omissions or mistakes in therapy are unavoidable. The important thing is to be perceptive enough to recognize such errors, understand how they came about, and undo them in a way that does not invite pleas of *mea culpa* from the participants but, rather, weaves the errors back into the thrust of the therapy.

One argument in favor of using audiovisual devices and of having the supervisor interview the patient is that these two methods can diminish the ambiguity inherent in the supervisory situation by providing a more accurate picture of what is happening in the therapy. However, the gain in accuracy may be offset by a loss in authenticity. When the supervisor sees the therapist's patient, either during the therapy or before it starts, it is a momentous occasion for the patient, whose response may be quite different from that elicited by the therapist.

The question of accuracy versus authenticity becomes even sharper when a recording device is introduced. The first of the earlier articles on privacy (1) mentioned that when the process notes of a therapist were compared with a recording of the interview, many discrepancies were found. The inference was that a self-report is not as trustworthy as a recording. That same article described situations in which therapists were audiotaped, videotaped, or observed from behind a one-way screen. In each instance, the experience of the therapist who was sitting with the patient was different from what the observer reported. In one case, when the original therapist was replaced by another therapist who had been an observer, the new therapist found that after he entered the room, his view of what was going on was closer to that of the original therapist. The new therapist stated that he had looked forward to putting his own ideas into practice and that he was quite unprepared for his change of view.

Recording devices and one-way screens may easily miss the subtle "feel" of the situation between two people who are face to face. As Ekstein and Wallerstein pointed out in 1958 (4), "the more such recordings approach 'verbatim accounts' in pursuit of the illusion that everything is captured, the more they tend to ignore the therapist's inner affective and cognitive responses to the patient's material as well as all the elements that comprise the emotional climate, the feeling of the impact two individuals made upon one another."

Further, the therapist's own report may provide an experienced supervisor with a more complete and authentic picture of the therapy than these devices can provide. A therapist's reluctance, for example, to include in the process notes much of what he or she said to the patient can be illuminating. Is such withholding characteristic of the trainee, or is it specific to the occasion? Again, when experienced supervisors, who can usually understand patients reasonably well through trainees' process notes, find themselves at a loss, they know they are dealing with a therapeutic impasse or with a patient whose personal definition may be the problem. For example, a 3rd-year resident treating a borderline patient whose thought processes were quite fragmented found it extremely difficult to piece together the process, even when he made notes immediately after each session. Concerned that he was not providing "good enough" material for his supervisor, whom he experienced as critical, he suggested that the sessions be taped so that both he and the supervisor could have a clearer idea of what was happening. The supervisor agreed that it was hard for him as well as for the resident to understand what the patient was expressing, but that it was exactly this quality of confusion which had to be worked out and understood, not seen as an obstacle to be overcome.

In short, instead of achieving the desired objectivity, recording devices and one-way screens may increase or shift the location of defensiveness. The self-consciousness of the therapist who knows that he or she is being observed moves from the interaction with the supervisor to the interaction with the patient. What may appear to be objectivity may in fact be a more far-reaching restrictiveness because the therapist feels more inclined to "follow orders" at the cost of his or her natural style. As for the supervisor, he or she may feel that all the material is at hand and thus be more likely to impose definitive prescriptions on the trainee. The patient, too, may experience changes in emphasis or direction from the therapist, changes that do not feel organic to the situation. As a result, both patient and therapist, unsure of their own steps and of each other's rhythms, tighten up and dance less freely.

INSTITUTIONAL AND PROFESSIONAL STRUCTURES AND PRIVACY

Another factor that contributes to the complex balance of the supervisory relationship has already been mentioned in the second of the earlier articles on privacy (2). Although it is possible to transfer what one learns about oneself in therapy from the therapy to other relationships, it is not possible to transfer the special quality of intimacy that may be achieved within a therapeutic relationship. Therapy is a partial relationship, and knowledge about both the therapist and the therapeutic relationship must usually be segregated from the rest of the patient's life. Supervision shares a measure of the intimacy of therapy because of the personal revelation of the therapist, but it does not share the segregation. Most training institutions encourage faculty and students to see one another outside the formal supervisory setting, and a stated goal of the supervision is to prepare the student to become a colleague and supervisor. The role conflict and discomfort that can result were mentioned in the series of faculty meetings we have described. Supervision occurs, for both therapist and supervisor, within a professional community where membership must be earned and maintained in order to gain acceptance and status, to make a living, and to participate in the community's cultural life.

For the supervisor, participating in the teaching process is a sign of status and acceptance by the professional community. As we have already pointed out, rigidity and dogmatism often mask the extreme complexity and ambiguity of the supervisory experience. The discrepancy between the personal freedom inherent in what is being taught and the rigidity of the teaching process is often unacknowledged. For trainees, this conflict is far greater and more complex. They want to learn to do therapy, but doing it well entails exercising considerable freedom within the therapeutic situation. If they are taught how to perform in a fairly dogmatic way, their efforts to learn interfere with this freedom.

Many disciplines besides mental health include a supervisory as well as a didactic experience, but there are

few in which the prime instrument to be tuned is the essential nature of an individual rather than a particular talent. Even in the arts, a book, a painting, or a dramatic role interposes a tangible product between the originator and the audience. In therapy the shared task is to maximize the revelation of the essence of one of its participants, and this procedure brings out the nature of the other participant as well. Becoming a good therapist may require a painful sorting out of one's natural inclinations. A good therapist comes to accept, at first on faith and then through experience, that spontaneity and self-expression must be harnessed for the sake of the therapy. One of the hardest things to learn is that channeling one's empathy into the proper objectivity requires a discipline which transforms customary social spontaneity into a friendly but more detached position in which self-indulgence is minimized.

The trainee may feel at times as if he or she is being asked to conform to institutional norms at the cost of creative personal expression. In fact, the teaching function of supervision does serve institutional goals, such as providing therapy that meets certain ethical and qualitative standards. Supervision gives the trainee an opportunity to recognize the extent to which theoretical and clinical knowledge can help in understanding the patient's associations and in informing the timing, phrasing, and purpose of the therapist's own actions. But all this erudition can only be gained at a price, the price of learning to rely on and be loyal to the supervisor, to the organization providing the supervision, and to the principles being espoused. Especially in psychoanalytic training, the period of such socialization and dependency can seem almost interminable.

One way in which most training institutions try to counter the inevitable demand on trainees to conform to a rigid outlook and help them retain their originality is to give them several supervisors. The trainees can then see that seasoned and well-trained people may arrive at different conclusions, techniques, and perceptions even when operating from the same underlying theoretical base. By experimenting with these different approaches, the trainee can begin to develop the style that is best suited to his or her unique outlook and personality. Most of the supervisors who attended the nine faculty meetings we held stated that they are deliberately self-disclosing; some tell personal anecdotes, some discuss their own therapeutic mistakes, and others try to show how they have reached their current theoretical positions. Few of them retain an aloof posture. By contrast, a supervisor who rigidly emphasizes analysis of the countertransference may exacerbate trainees' feelings of being under a microscope rather than show them that there are many lenses through which they can view psychotherapy.

We are not advocating a strict Viennese position, because we believe that good supervision must include a certain measure of learning about oneself as well as learning about therapy. Donald Meyer, for instance, suggests that supervisors convey the idea that introspection is part of professional development, thereby normalizing their trainees' personal reactions to their work (lecture presented at The Cambridge Hospital, Dec. 6, 1986). He also suggests that supervisors confine the range of personal exploration to issues directly related to the patient's treatment.

There are pros and cons to both models of supervision, which never exist in pure form but rather constitute a continuum that is mediated by the clinical and life experiences of each supervisor, with all of his or her individual idiosyncrasies. For the purposes of exposition, however, the two models will be described as if they were distinct entities.

The countertransference model of supervision may best facilitate trainees' learning about their unconscious motivations and the fit between their own psychodynamics and those of their patients. This enables the trainee to fine-tune his or her "third ear." Affectively charged learning that brings about changes in both the trainee and the patient can occur, and the supervisor will be provided with a richness of material that would be unavailable if he or she avoided exploration of the trainee's personal reactions. In this model, the trainee learns to recognize meaningful patterns through the resonances among the patient's verbal and nonverbal presentations, the trainee's own inner experience, and the "parallel process" that occurs in supervision. The risks inherent in too zealous an application of this model include interfering with the establishment of the rhythms and boundaries essential to both therapy and supervision, the crowding out of the trainee's ingenuity, and a subtle loss of authenticity as the supervisor's probing infringes on the privacy of the therapy and heightens the trainee's defensiveness. The trainee may fail to learn an appreciation and respect for the slow unfolding of resistance.

On the other hand, the didactic model of supervision facilitates trainees' acquisition of a body of knowledge that can provide a reassuring and clarifying template which they can hold on to while learning proceeds—a cognitive scaffolding. Such learning tends to be more cognitive than affective, and the supervisor is less likely to evoke shame and defensiveness in the trainee. Recognition of patterns by the trainee occurs through the supervisor's pointing out the repetitive aspects of the patient's ways of dealing with the world and the linkage of such observations to a body of theory. Too rigid an application of this model tends to result in an intellectualized and dry exercise that does not touch the trainee deeply. Thus, the trainee feels alone with his or her personal responses to the patient. The trainee may come to respect resistance too much, shying away from affectively charged clinical material.

Certainly, no single model of supervision, and no one style of doing therapy, is well suited to everyone. Neither eclecticism nor orthodoxy is ultimately as helpful as having each supervisor develop what works best for him or her. Trainees have more to gain if the dialectic between the personal and the didactic is not

fully resolved, so that they have the opportunity to experience the different ways in which a number of supervisors have achieved their own integrations. We would only suggest that supervision, though differing in many ways from psychotherapy, shares with it the need for a boundary, or at least a door. For in a situation where trainees' personal space may be invaded by supervisors, patients, and the institution, they may feel safe enough to learn only if they know that there are limits to the invasion of their privacy.

Finally, how do other professional and institutional structures that include supervision deal with the problem of privacy? Simmel's (15) analysis of secret societies and of the distinctive forms of organization that arise when the maintenance of secrecy is an important precondition sheds light on the general relationship between privacy and supervision. Simmel suggested that individuals need a balance of freedom and law. Secret societies, because of their autonomy and seclusion from the larger society, require an internal complement of formal coercion; thus, they tend to be highly ritualistic and to suppress individuality among their members. Rustin (16) applied these concepts to psychoanalysis, where maintenance of the patient's privacy or secrecy is crucial. As Rustin pointed out,

> The problem with this tension between the creative and the rule-ful, the private and the public, the work of the analytic dyad and the institutional structure in which it is contained, is that it seems impossible to resolve it wholly in favour of either pole, tempting as the contending claims of institutionalization and of individual freedom will sometimes be. Without a containing structure, there is no chance that the delicate and differentiated capacities needed to conduct analysis will be consistently nurtured. Yet such institutions are all too likely to fear the originality inherent in the process they are intended to further, and discriminate in favour not of the most alive, but of the most orthodox and safe representation of institutional continuity. (16, p. 146)

Simmel's and Rustin's work indicates that not only are there inherent tensions between institutional conservatism and creativity, since both structure and freedom are necessary in therapy as well as in supervision, but in the secret society of psychoanalysis, powerful and unconscious *sociological* processes are at work, which affect our attitudes toward the privacy of the patient and the trainee. Therapists and their supervisors may settle for and even seek to promote intrusions on privacy as well as conformity to rigid standards of practice in order to balance the ambiguous, free-form, and partially unpredictable nature of the work in which they are engaged.

As Simmel said, "The secret produces an immense enlargement of life. It offers the possibility of a second world alongside the manifest world." When applied to psychotherapy, these evocative words can be understood in two ways. The two-person secret society of patient and therapist, by virtue of the confidentiality surrounding whatever secrets are shared between them, becomes a "second world." But there are also secrets that a patient, consciously or unconsciously, keeps *from* the therapist. As discussed in the second of the earlier articles on privacy (2), even if a therapist asks for complete openness, the patient has certain means of maintaining privacy, such as nuance, gesture, and timing. The essence of the therapeutic process is better described as the slow abandonment of this secrecy than as stark openness. In this sense, secrecy—or resistance, as it is sometimes called—is a precondition for understanding.

The supervisor-therapist dyad, with its fragile component of privacy, also shares some of the features of a secret society. The trainee who resists supervision or distorts his or her process notes is using one of the ways of developing a second world in supervision. A recorded interview or the supervisor's interviewing of a patient certainly has a place, but these procedures carry costs as well as benefits. The openness and greater accuracy obtained from the use of recordings in supervision seems so self-evident, especially from a research point of view, that it may obscure the cost of upsetting the balance in training between reliability and originality. Similarly, helping the trainee develop greater personal awareness may seem so essential that it can be used to justify any intrusion on his or her privacy.

The call for therapists or supervisors to recognize the importance, even the necessity, of a measure of privacy for patients and trainees may trouble some people, and, certainly, if this idea of secrecy were to be applied too broadly, little learning would occur and little mutual confidence would be established. All that we are pleading for here is a narrow band of privacy, which, far from being the enemy of supervision, may be an essential ingredient of it.

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The deaths of these members were reported to APA between Feb. 27 and April 21, 1988.

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Possible Role of Antidepressants in Precipitating Mania and Hypomania in Recurrent Depression

David J. Kupfer, M.D., Linda L. Carpenter, B.A., and Ellen Frank, Ph.D.

This prospective study examined the incidence of mania or hypomania in 230 patients with recurrent depression treated with imipramine. Overall, only six individuals (2.6%) developed hypomania, representing 0.9% of those in the acute phase and 2.5% of those in the continuation phase of drug treatment. Patients with a history of bipolar II depression (N=33) did not have a greater incidence of hypomania than those with unipolar depression (N=197). Younger patients did not switch to hypomania more rapidly than older ones, and women were not more likely to switch than men. Systematic assessment of mania, stringent diagnostic criteria, and the recurrent nature of the sample may account for this low incidence of hypomania compared to that reported by other investigators.

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Although there is a general consensus that the introduction of tricyclic antidepressants has dramatically improved the outcome of acute treatment of the depressive episode, several questions remain concerning the possible adverse effects of these compounds on mood over the short- and long-term. A number of reports (1–8) have suggested that tricyclic antidepressants tend to precipitate mania or hypomania, not only in bipolar patients, who by definition have a history of mania or hypomania, but also in unipolar patients, who have no such history. Furthermore, these drugs have been reported to increase the frequency of recurrences of affective episodes and to induce rapid cycling in bipolar patients (9–13).

Other investigators have explored this issue in bipolar disorders; however, our longitudinal study of recurrent unipolar and bipolar II depression provides an opportunity to examine 1) whether tricyclic antidepressants play a role in increasing the likelihood of mania or hypomania in patients with recurrent depression and 2) whether the frequency of recurrences is increased during maintenance treatment with tricyclic antidepressants. Since our longitudinal study of maintenance therapy is not finished, we can address more directly the first question.

At present, a controversy exists as to whether antidepressant drugs, which elevate mood, cause mania in patients with affective disorder (14). Studies in this area have been criticized for examining only acute treatment and not including continuation therapy, for failing to separate bipolar patients from unipolar patients diagnostically, and for not paying systematic attention to the actual incidence of mania but rather relying on unsystematic observations. Other criticisms suggest that patients who are at greatest risk for such adverse mood responses to antidepressants as mania or hypomania have been systematically excluded from studies by requiring that patients become stabilized during acute treatment to be included in study outcome data. Still other criticisms suggest that these studies represent retrospective searches rather than prospective data collection carried out in a controlled environment or within a controlled treatment trial. We took all of these issues into consideration in the design of our long-term treatment study of recurrent depression.

In our analyses of the 230 patients who entered our study in the acute treatment phase, we have examined the incidence of hypomania in all 230 patients. Specifically, not only have we paid attention to those pa-

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tients who completed the continuation phase and later entered maintenance treatment but we have also systematically examined the records of all those patients who were not entered into maintenance treatment but were declared nonresponders to tricyclic antidepressants. With respect to this latter sample, particular attention was paid to whether hypomania or mania represented a major reason for termination from the protocol or whether further treatment with additional or other medications resulted in hypomania.

METHOD

To enter the recurrent depression study, patients had to meet Research Diagnostic Criteria (RDC) (15) for a major primary affective disorder at the time of initial evaluation. In addition, all patients must have had at least one other major depressive episode during the prior 2½ years and one additional lifetime major depressive episode. Thus, all patients clearly met the criteria for recurrent depression. All previous episodes must have required psychiatric treatment or resulted in substantial functional impairment. All patients must have reported at least a 10-week period of remission between the index episode and their previous episode. Patients who had substantial cardiovascular, renal, liver, or endocrine disease, pregnancy, epilepsy, glaucoma, organic brain syndrome, or mental retardation or a medical history that would preclude the use of tricyclic antidepressants were excluded from the study. Furthermore, the index episode could not be secondary (concurrent or subsequent) to any other psychiatric or medical illness within 2½ years. Specifically excluded were the following disorders as defined by the RDC: schizophrenia, schizoaffective disorder, unspecified functional psychosis, alcohol abuse, and drug abuse.

All patients were given physical and neurological examinations and were kept free from any psychotropic drugs for at least 14 days before the initial psychiatric, EEG sleep, and neuroendocrine evaluations, which preceded entry into the study. Patients had a comprehensive independent assessment to ascertain whether they met severity criteria for the investigation including a Hamilton Rating Scale for Depression score of 15 or greater (by a single rater on the 17-item version) and a total of 7 or greater on the depression part of the Raskin Severity of Depression and Mania Scale (16).

After the initial evaluation, all patients received the same acute treatment regimen, which consisted of combined pharmacotherapy (imipramine, 150–300 mg/day) and interpersonal psychotherapy (17). An attempt was made to treat all patients with 200 mg/day of imipramine, and adjustments during the acute treatment phase were carried out to maximize clinical efficacy or reduce adverse effects (the majority of patients responded to the 200-mg/day imipramine regimen). Patients were seen weekly for the first 12 weeks, every other week for the next 8 weeks, and then monthly until they had completed a continuation treatment period of 20 weeks during which their drug dose did not change and their rating scale scores remained stable and consistent with a clinical remission (Hamilton scale score of ≤ 7; Raskin depression scale score of ≤ 5). Additional crisis sessions were held when a patient's condition between regularly scheduled visits warranted further clinical attention. At every clinic visit, patients were interviewed by an independent clinician who evaluated them using the Hamilton scale, the Raskin depression scale, and the Raskin mania scale. Also at each clinic visit an extensive progress note on the patient's condition and progress to date was completed by the two members of the treatment team: the primary clinician (nonpsychiatrist) and a psychiatrist. These procedures (completion of Hamilton and Raskin scales and progress notes) were systematically carried out at every patient contact, including many crisis sessions. Telephone consultations with clinic staff made by patients or significant others were documented in the charts and commented on in subsequent progress notes.

For the purposes of this study, a patient was considered to be hypomanic if two criteria were met: 1) a score of 4 or greater on the Raskin mania scale and 2) some note of hypomanic symptoms in the progress notes made by the clinicians on the date of contact when mania was considered present according to the Raskin mania scale. The Raskin mania scale provides scores on each of three dimensions (verbal report, behavior, and other symptoms) from 1 (not at all evident) to 5 (very much evident), so total scores for the scale range from 3 to 15. We chose a score of 4, indicating manic behavior "somewhat" evident on only one dimension, as our initial screening criterion for possible hypomania. Further examination of every instance in which a score of 4 or greater was recorded ensured that no cases of hypomania would be left uninvestigated. Because increased energy and mood are normal manifestations of recovery from a depressive episode and might result in a Raskin mania scale score of 4, we checked progress notes to determine which occasions included hypomanic symptoms. Indications by family or friends of a patient's hypomanic behavior were also taken into consideration (although these usually resulted in a clinician-initiated crisis session). Combining the Raskin mania scale scores with progress notes provided a high level of confidence that we had not failed to identify any patients who met RDC descriptive requirements for a probable hypomanic episode. Although chart review of symptoms or picking an arbitrary cutoff score on a rating scale are techniques that have been used alone, we opted to improve the precision of our analysis by linking the two methods. Other investigators (18) have also required both a minimum mania scale rating and documentation in the medical record of behavior and symptoms when assessing hypomania. Given the often subtle nature of hypomania (relative to symptoms of depression or mania), we felt a less stringent initial criterion (a

score of 4 on the Raskin mania scale) with a more thorough follow-up for potential cases of hypomania (chart review of progress notes) would best serve to determine an accurate rate of hypomania among our patients. In fact, all six patients with hypomania had a minimum Raskin score of 5.

As mentioned earlier, this study concentrated only on the incidence of hypomania during the premaintenance (acute and continuation treatment) phases of the study. Background information collected via the Schedule for Affective Disorders and Schizophrenia (SADS) (19), which was administered at the time of initial screening and again when patients had recovered from their index episodes, was used on conjunction with data from the lifetime history of affective disorders interview (developed specifically for this protocol) to determine which patients had ever met RDC for bipolar II depression.

Because of the nature of the findings, i.e., the fact that the number of patients experiencing hypomania was small, the results are presented with descriptive statistics alone. Each of the six patients with hypomania is described to illustrate when the hypomanic symptoms occurred in the course of the depressive episode.

RESULTS

Our patient sample (N=230) can be characterized in the following way: 180 (78.3%) were women, 39 (17.0%) were single, 129 (56.1%) were married or living with a partner, and 62 (27.0%) were separated, divorced, or widowed. A third of the sample (N=76) had at least graduated from college, 36.1% (N=83) had completed some college, and 30.9% (N=71) had a high school education or less. The mean±SD age of the patients was 39.5±10.6 years, and the mean±SD age at onset of their first episode of major depression was 27.0±10.6 years. Their mean±SD number of previous episodes was 6.2±6.0; their mean±SD duration of index episodes was 23.2±17.2 weeks, and their mean±SD Hamilton depression score at entry into the study was 22.1±4.6. Over 90% of the patients (N=208) met RDC "definite" or "probable" status for endogenous subtype. The patients' mean±SD time in premaintenance (acute and continuation) treatment was 46.8±33.6 weeks.

Of the 230 patients who entered the study, only six (2.6%) developed hypomania, and none experienced mania. During the initial 16 weeks of acute treatment, two individuals (0.9%) became hypomanic. Of the 157 patients who entered the continuation treatment phase, 4 (2.5%) became hypomanic. Of the 230 patients entered into the acute phase, 33 (14.3%) had a history of bipolar II depression; of the 157 patients entered into the continuation phase, 24 (15.3%) had a previous bipolar II diagnosis. The group of bipolar II patients in the sample did not have a greater incidence of hypomania than did the group with recurrent unipolar depression (one of 33 or 3.0% versus five of 197 or 2.5%).

Younger patients did not switch to hypomania more rapidly than older patients. The ages of the hypomanic patients ranged from 25 to 60 years, with no age-related pattern in amount of time before hypomanic symptoms occurred. A greater incidence of hypomania in women was not observed; three (1.7%) of 180 women and three (6.0%) of 50 men became hypomanic. Summary information about the six patients who developed hypomania follows.

CASE VIGNETTES

Case 1. A 60-year-old man suffered a relapse after having initially completed the acute and continuation treatment phases of the protocol. He was treated acutely again and had just begun to stabilize a second time when his hypomanic episode occurred; he had symptoms of increased energy, mood, and libido and decreased need for sleep. He had been taking 200 mg/day of imipramine for 17 weeks by the time he became hypomanic. After his hypomania subsided, he entered the continuation treatment phase but was terminated from the protocol when he relapsed again.

Case 2. A 51-year-old woman entered the protocol and was being treated in the acute phase with imipramine for 1 month before the drug was discontinued when she developed medical complications (changes in ECG and abnormal cardiac symptoms). She became hypomanic 1 week after the medication was stopped, experiencing rapid speech and a marked decrease in need for sleep. She was soon discontinued from the protocol as a result of her medical problems.

Case 3. A 26-year-old woman was treated with imipramine for 6 months (through the acute and the continuation phases) before she developed intolerable side effects and the medication was discontinued. Two weeks after she was withdrawn from imipramine she became irritable and experienced grandiosity, impulsive behavior and spending, and pressured speech. She was eventually discontinued from the protocol as a result of the side effects she was experiencing.

Case 4. A 41-year-old man (with a past diagnosis of bipolar II depression) completed all premaintenance phases of the study and thus had been taking imipramine for over 1 year before his drug dose was tapered in preparation for entry into a maintenance phase in which he was given placebo pills. In this transition period, he became hypomanic as imipramine was discontinued. His symptoms were decreased sleep, heightened libido, energy, and activity, and inflated self-esteem. However, he eventually entered the maintenance treatment phase.

Case 5. A 25-year-old man had been taking 250 mg/day of imipramine for 9 weeks, becoming hypomanic during the acute phase. The hypomanic episode was very brief, characterized by mood swings, irritability, increased libido and activity, and diminished need for sleep. He continued in the protocol through the maintenance treatment phase before being discontinued for noncompliance.

Case 6. A 30-year-old woman was taking imipramine for 8½ months (completing both premaintenance phases) before her medication was tapered in preparation for maintenance treatment that provided psychotherapy alone. She became hypomanic as soon as the imipramine was discontinued. The hypomanic symptoms (increased energy, libido, and spending, pressured and loud speech, and trouble falling asleep) subsided, and she remained in the protocol in the maintenance treatment phase.

DISCUSSION

Bunney (6) and Murphy (5) have suggested that antidepressants induce mania or hypomania in an average of 9% of patients treated acutely for depression. The 12 prospective, placebo-controlled studies reviewed by these authors were carried out before unipolar and bipolar patients were examined separately; hence, their results may have been inflated by the presence of small numbers of bipolar patients in the samples. Patients in these studies became hypomanic rather than manic. Van Scheyen and Van Kammen (7) carried out an uncontrolled, nonblind study and reported that 25% of unipolar patients treated with tricyclics alone switched into mania 15–57 days after the initiation of pharmacotherapy. These authors suggested that the switches occurred more rapidly in younger patients than in older ones and more often with clomipramine than with amitriptyline.

The results of the present study indicate an incidence of hypomania considerably lower than any reported in previous literature. Overall, only 2.6% (N=6) of the entire 230 recurrent depressed patients in our protocol became hypomanic. Furthermore, patients with a past history of bipolar II depression did not show a higher incidence of switching than the "pure" unipolar patients, contrary to what we might have expected given the higher incidences of switching that have been reported for bipolar patients (8). Although other investigators (13, 20) have found women to be at a higher risk than men for drug-induced mania among bipolar patients, we did not observe such a pattern in our sample. Additionally, we were not able to replicate the finding of Van Scheyen and Van Kammen (7) that younger unipolar patients experienced a more rapid onset of hypomania than older unipolar patients. Finally, we noted that four of the six (67%) switches to hypomania in our study occurred at the time treatment with imipramine was discontinued. Hypomania during withdrawal of antidepressants is an observation that has been reported by others (21, 22).

A number of features distinguish this study from previous research on the mania-inducing effects of antidepressant medications. First, the maintenance therapies protocol was prospectively designed to systematically evaluate mania at every patient contact. Assessments with the Raskin mania scale and the clinicians' routine alertness to, and observation of, hypomanic symptoms assured a thorough and consistent documentation of the incidence of switching. Second, diagnostic procedures specifically eliminated all bipolar I patients and also allowed us to identify for separate consideration those among our patients with recurrent depression who had previously met RDC for bipolar II illness. Because of our stringent inclusion criteria, we can be confident the depression of all 230 patients is homogeneous with respect to its recurrent nature (at least three depressive episodes) and absence of organic or substance abuse illnesses. Third, our sample represents the largest group of patients examined in a study of this type. All 230 patients were given the same drug at approximately the same dose with the same adjunct psychotherapy—all in one setting. Patients most at risk for adverse effects from imipramine were not excluded from the study, since our nonresponders were also followed after they discontinued the protocol. Any or all of these factors may account for the uniqueness of our findings.

In interpreting the results of our study in relation to the higher incidences of switching reported by other researchers, we conclude that our study represents a more accurate reflection of clinical practice than has previously been available. The Collaborative Study on the Psychobiology of Depression also reported no cases of hypomania or mania during short-term treatment with imipramine or amitriptyline in over 100 unipolar depressed patients (personal communication). Perhaps more careful titration of tricyclic medication or other improvements in current treatment contributed to the low incidence of hypomania in our sample. Alternatively, one might hypothesize that the recurrent nature of our sample somehow lessens the proneness of these patients to mania or hypomania. Bipolar patients who have experienced only one or two episodes of depression may be more prone to switch into mania or hypomania if given tricyclics than patients who have had multiple depressive episodes. Our patients had experienced a relatively high average of 6.2 prior depressive episodes, a characteristic that distinguishes our sample from the samples in similar studies. Even those patients in our sample who had been hypomanic (bipolar II) appeared to have "burned out" their tendency to switch, at least while taking tricyclic medication. Further studies correlating the rate of switching with number of previous episodes are needed to appropriately test this hypothesis.

Several clinical implications arise from these results. Clearly, clinicians should not hesitate to treat recurrent unipolar patients with tricyclic medications. In the case of a depressed individual who has a history of hypomania, the presence of several more recent recurrent depressive episodes suggests that the patient is not at great risk for switching when antidepressants are administered. Additionally, our observations of the six hypomanic patients in this study indicate that physicians should be alert to symptoms of hypomania or mania at the time that medication is discontinued. In the six patients we studied, the hypomanic episodes

were very brief and did not alter the overall course or treatment of depression.

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The Amphetamine Challenge Test in Patients With Borderline Disorder

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The authors used amphetamine as a psychopharmacological probe to investigate the hypothesis that patients with borderline personality disorder are prone to psychosis following ingestion of a dopamine agonist. Sixteen patients with borderline personality disorder participated in the study. Significant increases in the mean total Brief Psychiatric Rating Scale scores and in activation and thought disturbance factors after amphetamine administration were noted in the sample. Patients with diagnoses of both schizotypal and borderline personality disorders worsened transiently with amphetamine administration, but patients with only the borderline diagnosis improved. These results indicate the usefulness of pharmacological probes to further understand DSM-III *axis II disorders.*

(Am J Psychiatry 1988; 145:809–814)

Modern clinical investigation of borderline personality disorder began in the late 1970s following the introduction of specific diagnostic instruments such as the Diagnostic Interview for Borderline Patients (1). There had been a controversy about the nature of the disorder based on its clinical phenomenology, but newer investigative tools—such as the dexamethasone suppression test (DST) and sleep EEG studies—led to further discussion of the biological nature of the disorder.

Two major schools of thought about borderline personality disorder (in its pre-*DSM-III* conceptualization) focused on its relationship to either schizophrenia or affective disorder. Those who espoused the relationship to schizophrenia cited the genetic literature, which demonstrated borderline schizophrenia in the families of schizophrenic patients (2); the brief psychotic episodes or mild psychotic symptoms seen in borderline patients (3, 4); the response of borderline patients to unstructured psychological tests such as the Rorschach, shown to be like the response of schizophrenic patients (5, 6); and the response of borderline patients to antipsychotic medications (7–11). The proponents of the relationship of borderline personality disorder to affective disorder noted the higher morbid risk of affective disorder in relatives of borderline patients (12–15), sleep EEG findings (shortened REM latency) similar to those in depressed patients (16–19), escape from cortisol suppression in response to dexamethasone in most (20) but not all (21) borderline patients, and response of a similar disorder—emotionally unstable character disorder—to lithium carbonate (22).

Phenomenologically, the broad concept of borderline personality disorder was divided into two parts by *DSM-III*; the process of this division has been described by Spitzer et al. (23). As specific criteria for schizotypal personality disorder and instruments to make diagnostic assessments became available, further refinement of the heterogeneity of borderline disorders could be made.

Challenge strategies have been useful in medicine in further clarifying diagnostic issues. In psychiatry lactate infusion studies represent a paradigm in which patients' symptoms are induced by the infusion (24) and the pathophysiology of panic is then explored (25). Amphetamine testing has been used for decades to better understand a number of mental illnesses, including schizophrenia and depression. Schizophrenic patients often respond to amphetamine or methylphenidate with a transient exacerbation of psychosis (26–28). This response appears more frequently in schizophrenic patients with positive symptoms (29) and in those with normal-sized ventricles (Goldberg et al., personal communication) and may be correlated with response to neuroleptics (30, 31). Patients with depression also have a heterogeneous response to amphetamine (32), which may be related to their response to antidepressants (33, 34). Three studies of normal subjects (35–37) found a mild elevation in mood following doses of amphetamine or methylphenidate similar to those used in the study described here. However, one study (38) found that previous amphetamine abusers had a psychotic response to much higher

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doses. Because of these studies, administration of amphetamine to borderline patients appeared to be a new strategy to explore the characteristics of borderline personality disorder.

The current study was designed to extend our earlier finding that four of eight patients with borderline personality disorder had symptoms of psychosis following amphetamine challenge (39). In the current experiment, the sample is larger (16 patients with borderline personality disorder) and the subjects received more complete clinical evaluation. The first author (S.C.S.) did not participate in patient selection, so this possible means of bias was avoided. Our current hypothesis was that *d*-amphetamine would act as a psychopharmacological probe in borderline patients to identify more discrete subgroups of patients with personality disorder. More specifically, we hypothesized that some borderline patients would be susceptible to psychosis after ingesting amphetamine.

METHOD

Patients for this study were recruited through Mood Disorders Unit-10, a section of the Affective Disorders Module at Western Psychiatric Institute and Clinic. Patients in whom borderline personality disorder was suspected were then seen by the project coordinator (P.M.S.), who administered the Diagnostic Interview for Borderline Patients (1). Patients were eligible for the study if their score was 7 or greater (definite borderline by Diagnostic Interview for Borderline Patients criteria) and they did not have schizophrenia, manic-depressive disorder, or medical illness. However, major depression was not an exclusion criterion. The axis I assessment was made by using the Schedule for Affective Disorders and Schizophrenia (SADS) (40). Patients were also evaluated for schizotypal personality disorder by using a symptom checklist (41). Eighteen patients were found to be eligible for the study and signed informed consent documents. One patient became too upset to participate during the setup procedure and was not studied, and another patient dropped out after one session in which she received placebo, leaving a study sample of 16 patients. All 16 patients received amphetamine and 13 received both amphetamine and placebo.

The 16 patients studied included nine women and seven men; their mean±SD age was 26.1±5.5 years. As mentioned, all had a Diagnostic Interview for Borderline Patients score of 7 or more; their mean±SD score was 8.1±0.8. Eight of the 16 patients also met *DSM-III* criteria for schizotypal personality disorder. All patients had been on the inpatient service for at least 1 week and had not received psychotropic medications during that time. None of the patients had been receiving regular treatment with neuroleptics, antidepressants, or benzodiazepines before admission.

The amphetamine challenge study was a double-blind, placebo-controlled experiment in which either *d*-amphetamine, 30 mg, or placebo in identical capsules was administered orally in random order, always at 9:00 a.m. The random assignment was determined by the research pharmacist. Of the 16 patients studied, eight received placebo then amphetamine, five received amphetamine then placebo, and three received amphetamine alone. Patients were studied in the EEG laboratory, where both EEG and neuroendocrine studies were simultaneously performed with the behavioral assessment (these studies will be reported in another paper). Two psychiatrists (S.C.S. and J.C.) were present at each session and performed the behavioral ratings. The ratings were scored by consensus of the two doctors, who were blind to the Diagnostic Interview for Borderline Patients scores, SADS evaluation, and schizotypal classification. Neither patients nor raters knew whether amphetamine or placebo was being administered. On the test days the raters completed the Brief Psychiatric Rating Scale (BPRS), modified by Bigelow and Murphy (unpublished 1976 paper) to include anchor points for specific behaviors, and the Clinical Global Impression (CGI) at 9:00 a.m. before administering capsules and at the end of each session at 11:00 a.m. At baseline (9:00 a.m.) and at 10:00 a.m., 10:30 a.m., and 11:00 a.m. (end point) the patients completed the SCL-90 and a global assessment of well-being on a scale of 1–100 on which 1=worst you've ever felt and 100=best you've ever felt. Patients then returned to the ward.

Three patients received amphetamine only. The placebo comparison of two of these patients was cancelled because they became transiently psychotic during testing and were given a neuroleptic. The other patient did not receive placebo because of a medical problem.

The analysis of the data began by an examination of the main hypothesis, which was that the effect of amphetamine on behavior would be different from the effect of placebo. This was done by paired t tests for the total BPRS scores and the BPRS factors. As already noted, some patients received only amphetamine; therefore, to examine their response, paired t tests comparing their baseline values to their end-point values were used. Inspection of the individual responses to amphetamine revealed the possibility of a biphasic response to amphetamine compared with placebo, supported by one-group chi-square analysis with Yates' correction. The post hoc hypothesis that the biphasic response was associated with differences in the responses of patients with borderline personality disorder versus those with borderline personality disorder plus schizotypal personality disorder was explored by using two-tailed independent t tests.

RESULTS

The behavioral results of the experiment will be reported in three parts. First we will discuss the global

TABLE 1. BPRS Scores of 16 Patients With Borderline Personality Disorder Before and After Receiving Amphetamine

BPRS Factor	Baseline Mean	Baseline SD	End Point Mean	End Point SD	t (df=15)[a]	p
Anxiety-depression	7.3	1.6	9.3	4.0	1.96	0.06
Anergia	5.0	1.8	4.6	1.6	1.46	0.16
Thought disturbance	4.1	0.3	6.5	2.4	3.98	0.001
Activation	3.7	0.7	6.1	2.2	4.23	0.001
Hostile-suspiciousness	3.9	1.2	4.3	1.6	0.92	0.37
Total	31.5	3.5	40.0	9.7	3.30	0.004

[a]Paired t test.

TABLE 2. Change in BPRS Scores of 13 Patients With Borderline Personality Disorder Given Amphetamine and Placebo

BPRS Factor	Amphetamine Mean	Amphetamine SD	Placebo Mean	Placebo SD	t (df=12)[a]	p
Anxiety-depression	1.0	3.7	0.3	2.0	0.70	0.50
Anergia	−0.5	1.0	0.3	3.4	0.84	0.42
Thought disturbance	1.9	2.2	0.0	0.4	3.04	0.01
Activation	1.8	1.7	−0.6	0.9	3.58	0.003
Hostile-suspiciousness	−0.1	1.3	0.3	1.2	0.60	0.56
Total	5.2	8.1	−0.3	4.7	2.30	0.037

[a]Paired t test.

changes, then the specific symptom changes, and, finally, we will address the question of heterogeneity.

The total BPRS scores of the 16 patients who received amphetamine significantly increased from the baseline (9:00 a.m.) to the end-point (11:00 a.m.) assessments (see table 1). The change in total BPRS score was highly correlated with changes in the CGI. The increase in total BPRS scores for the 13 patients who had both amphetamine and placebo was significantly greater after amphetamine administration than it was after placebo (see table 2). This indicates that the increase in psychiatric symptoms was not secondary to the patients' expectations.

To determine the specific types of symptoms that were changed following amphetamine administration, the data for the individual BPRS factors were examined (42) (see tables 1 and 2). The two factors that were changed significantly following amphetamine administration were activation and thought disturbance (table 1). The anxiety-depression factor score increased by two points after amphetamine administration, but this increase just failed to reach significance (table 1). Both of the factor scores that were significantly higher after amphetamine administration were also significantly higher than they were after placebo administration. In the placebo-controlled examination of the BPRS factor data the amount of change in the anxiety-depression score was diminished. It is important to note that the increases in thought disturbance and activation scores following amphetamine administration were significantly greater in the placebo-controlled analysis even though two patients who had marked increases in thought disturbance following amphetamine administration could not be included.

In the earlier experiment in which amphetamine was given to patients with borderline personality disorder (39) some variability of response was noted, but the focus of that report was on susceptibility to psychotic symptoms. As more patients were studied, it appeared that most patients changed significantly but not always in the same direction. That is, some patients had transient worsening, usually characterized by psychotic symptoms, while others improved in a global sense, usually with a more optimistic and energetic outlook. The behavioral results were therefore analyzed to further explore the hypothesis that the response of borderline patients to amphetamine was heterogeneous.

The first step in this analysis was to examine the global outcome as measured by the CGI measurement performed at the end of each BPRS assessment. The CGI was chosen because both improvement and worsening can be scored with this instrument. Five of the 13 patients were rated as unchanged after the placebo condition; only one of the remaining patients was rated as more than minimally different (see figure 1). Following amphetamine administration, however, only one patient was rated as unchanged and 10 were rated as moderately, much, or very much different irrespective of direction of change (figure 1). After amphetamine administration four subjects were noticeably improved and six were noticeably worse (figure 1). A one-group chi-square analysis for the placebo condition revealed no significant difference from an expected distribution of the subjects ($\chi^2=0.45$, df=2, p=0.68). However, the same test showed the distribution of response to be significantly different from expected following amphetamine administration ($\chi^2=6.02$, df=2, p=0.048).

The next step in the analysis of the heterogeneity of outcome was to determine whether the diagnosis of schizotypal personality disorder was associated with worsening or emergence of psychosis. The patients were separated into those with borderline personality disorder only (N=8) and those who also fulfilled the *DSM-III* criteria for schizotypal disorder (N=8). The eight patients with borderline personality disorder plus schizotypal personality disorder had a significantly higher mean±SD total BPRS score at the end of the amphetamine day (46.1±9.2) than the eight patients with borderline personality disorder alone (33.9±6.8) (t=3.0, df=14, p=0.008; see figure 2). When the placebo scores were subtracted from the amphetamine scores (for the 13 patients who underwent both conditions), there was still a significant difference between the patients with borderline personality disorder and those with borderline personality disorder plus schizotypal personality disorder (t=2.47, df=11, p=0.03).

The increase in BPRS scores noted for the patients with borderline personality disorder plus schizotypal personality disorder was corroborated by the self-rated 1–100-point assessment of well-being. The patients with borderline personality disorder rated themselves a mean±SD of 9.2±16.4 points better after amphetamine administration than did those with borderline

FIGURE 1. Change in CGI Scores of Patients With Borderline Personality Disorder Only or Borderline and Schizotypal Personality Disorders After Receiving Placebo or Amphetamine

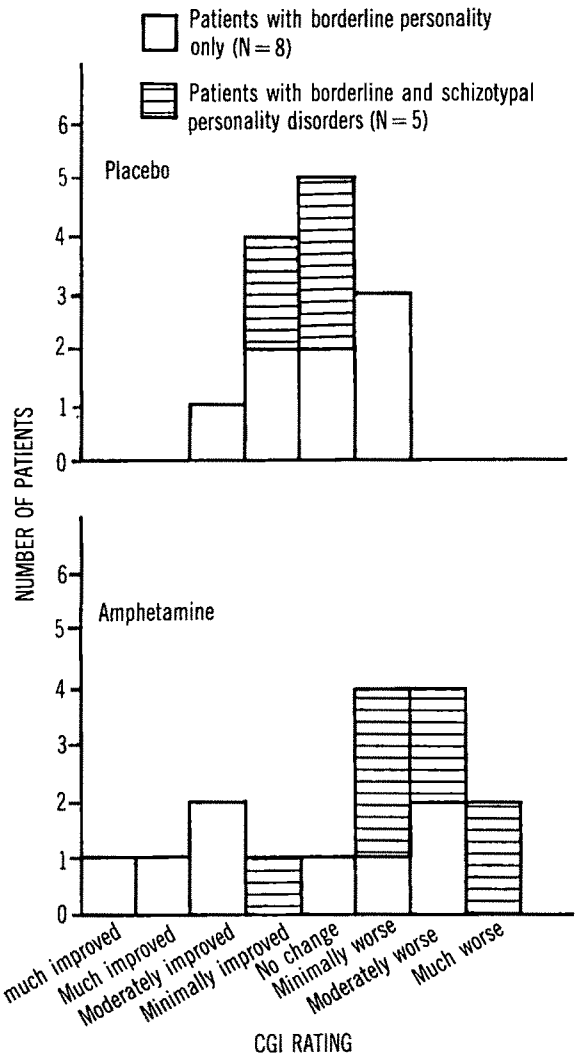
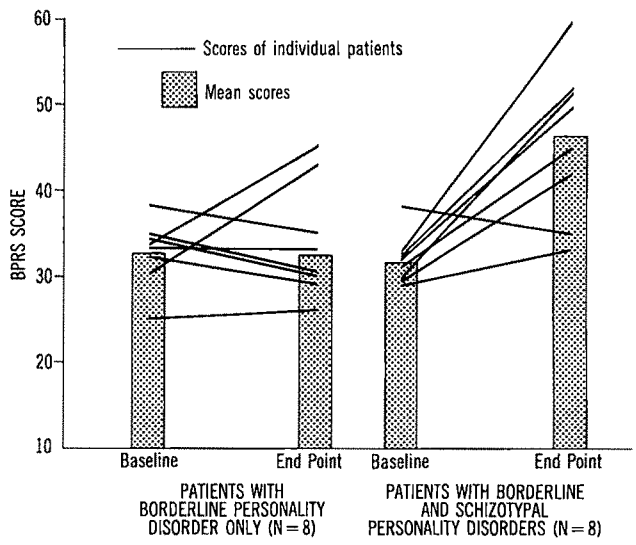


FIGURE 2. Total BPRS Scores of Patients With Borderline Personality Disorder Only or Borderline and Schizotypal Personality Disorders Before and After Receiving Amphetamine



personality disorder plus schizotypal personality disorder, who rated themselves 7.3±14.2 points worse (t=2.16, df=14, p=0.047).

Examining the factors of the BPRS revealed some differences between the borderline personality disorder alone and the borderline personality disorder plus schizotypal personality disorder categories. The patients with borderline personality disorder plus schizotypal personality disorder had more psychotic symptoms after receiving amphetamine than the patients with borderline personality disorder alone as rated by the BPRS thought disturbance factor (7.6±2.8 versus 5.4±1.4; t=1.99, df=14, p=0.06). The activation factor of the BPRS was not different for the two groups. It should be noted that the two groups were similar in baseline scores of the BPRS and its factors.

The patients with borderline personality disorder plus schizotypal personality disorder also had more psychotic symptoms after receiving amphetamine than the patients with borderline personality disorder alone according to their own self-ratings of psychoticism from the SCL-90 (10.8±9.6 versus 5.24±4.3; t=1.4, df=14, p=0.17). The patients also were assessed on axis I by SADS interview for both current and past psychiatric diagnosis. Neither present nor past history of depression was associated with being rated better or worse following amphetamine administration.

DISCUSSION

This study confirms the conclusions of our first report (39) that borderline patients change significantly following amphetamine administration in placebo-controlled experiments, including significant changes in the thought disturbance factor of the BPRS. It is also consistent with but not identical to the recent reports by Lucas et al. (43) and Kellner et al. (44), who reported the provocation of symptoms by methylphenidate and procaine, respectively.

Concerning the concept that the response to amphetamine is heterogeneous in borderline patients, this study shows that some patients have transient worsening following amphetamine administration (usually accompanied by psychotic symptoms), while others feel better. Of interest is the association of the dual diagnoses of borderline and schizotypal personality disorders with higher scores on the total BPRS, the activation and thought disturbance factors of the BPRS, and the psychoticism factor of the SCL-90 and worsening according to CGI assessments. It is of interest that the differences on more than one assessment were significant or nearly so, thus discounting a concern that the association of a rating outcome with diagnosis is a chance finding.

The finding that the borderline patients whose psychoses and feelings of well-being got worse after receiving the dopamine agonist amphetamine also had diagnoses of schizotypal personality disorder has face validity. Schizotypal patients are more prevalent in the families of schizophrenic patients than in the families of control subjects (2, 45) and have been shown to respond to low doses of dopamine-receptor-blocking neuroleptics (10, 11, 46). Worsening after amphetamine administration is also consistent with the observation that some borderline patients get worse when treated with amitriptyline (11). The study of patients with only the diagnosis of schizotypal personality disorder could further develop this hypothesis. Also, the subjects of this study did not have symptoms of thought disturbance before the amphetamine challenge and thus, unlike schizophrenic patients, the response was not an exacerbation of symptoms.

The increased thought disturbance in the patients with borderline personality disorder plus schizotypal personality disorder was paralleled by the global improvement of patients with borderline personality disorder who did not have schizotypal personality disorder. Even though the behavioral changes in all of the patients were not correlated with a SADS diagnosis of depression, three of the eight patients with borderline personality disorder had substantially increased energy and outlook following amphetamine administration. On the CGI the patients with borderline personality disorder were rated as improved and as a group had a 9.2-point increase in well-being on their self-rated 100-point form. This is consistent with hypotheses about the relationship of borderline personality disorder and affective disorders, which are supported by family (12, 14–16), neuroendocrine (20, 47), and sleep EEG (18, 19) studies. Even the dispute about this relationship (48) could be addressed by hypothesizing a subgroup of borderline subjects characterized by family members with depression, affective disturbance, response to tricyclics or monoamine oxidase inhibitors (MAOIs), and increased well-being in response to amphetamine administration. An alternative explanation about the response of patients with borderline personality disorder is that it is within the normal range as shown in the trials of normal subjects (35–37).

The thrust of this paper has been to view the borderline disorder from a medical model paradigm, as if it were a type of heterozygous disorder (49). This is not to ignore theories of maternal deprivation or important losses early in the patient's life, which happens statistically more frequently in the lives of patients with borderline personality disorder (50). Of interest to us are a series of experiments from the University of Wisconsin in which socially deprived monkeys were compared with standardly raised monkeys following amphetamine administration. The socially deprived monkeys were isolated early in life but then raised with other monkeys and were not different from their peers at 3–4 years of age. The isolated monkeys had a markedly different response to amphetamine, including a highly physically aggressive response (51; unpublished 1985 paper by W.T. McKinney et al.). It is possible, then, that through mechanisms not understood there is an enduring effect of early life experiences on primates and people which is not detectable in regular life but which is manifest in the laboratory with chemical challenge or under certain stresses.

An important concern about any challenge study that may lead to expression of symptoms—an ECG stress test, lactate infusion study, or amphetamine challenge—is whether it harms the patient. In this study of borderline and/or schizotypal patients, two subjects who worsened were given low doses of perphenazine; their symptoms rapidly resolved. Interestingly, a few subjects who had psychotic symptoms during testing found that the experience crystallized their need for treatment.

These results are consistent with categorizing patients with borderline personality disorder plus schizotypal personality disorder in the schizophrenia spectrum and associating borderline personality disorder with affective disorders. The amphetamine challenge or other chemical challenges (methylphenidate, L-dopa, fenfluramine, or procaine) can be useful research tools for investigating the pathophysiology and validity of the heterogeneity of personality disorders.

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The Epidemiology of Dysthymia in Five Communities: Rates, Risks, Comorbidity, and Treatment

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Data from a survey of five U.S. communities showed that dysthymia affected approximately 3% of the adult population. It was more common in women under age 65, unmarried persons, and young persons with low income and was associated with greater use of general health and psychiatric services and psychotropic drugs. Dysthymia had a high comorbidity with other psychiatric disorders, particularly major depression; only about 25%–30% of cases occur over a lifetime in the absence of other psychiatric disorders. The findings suggest that although the onset and highest risk periods of major depression and bipolar disorder are in young adulthood, a residual state of dysthymia occurs in middle and old age.

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There is general agreement that some portion of the general population and a relatively large proportion of people who seek advice from a physician have chronic, persistent low-grade symptoms of depression (1, 2, and unpublished 1986 work by J.D. Burke and D.A. Regier). While these symptoms may not meet the *DSM-III* criteria for major depression, they often result in considerable impairment of functioning and use of health care facilities. It is unclear precisely how prevalent these symptoms are and whether they constitute a separate psychiatric disorder, the residual or prodromal effects of major depression or other psychiatric or medical disorders, or the manifestation of a longstanding personality trait.

Until recently, the study of the precise nature and boundaries of these symptoms has been limited by variability in the definitions of chronic depressive states and by lack of population-based data. *DSM-III* clarified the definition by including descriptive criteria for dysthymia that are based on phenomenology. In addition, epidemiologic data on dysthymia are now available from a population sample that includes both treated and untreated persons with the disorder. Previous observations about dysthymia were based on select samples of persons coming to various treatment settings.

In this article we present data on the rates, risks, and comorbidity of dysthymia and the use of health services for its treatment in five communities in the United States. The data were derived from the NIMH Epidemiologic Catchment Area study, the overall goal of which is to estimate rates and correlates of psychiatric disorders and use of health services in a community sample. A full description of the purpose and methods of the study can be found elsewhere (3, 4).

METHOD

The Epidemiologic Catchment Area project consists of surveys in which comparable interview schedules and study designs are used to study the five communities: New Haven, Conn.; St. Louis, Mo.; Baltimore, Md.; Piedmont, N.C.; and Los Angeles, Calif. The communities vary considerably in size, population, and geographic location. The first wave of the study was conducted between 1980 and 1983. Using probability sampling techniques, workers at each site interviewed a representative sample of the residents who were 18 years of age or older. The total five-site community sample size was 18,572; response rates ranged from 68% to 79%. Reasons for nonresponse are explained in detail elsewhere (3, 5); the major reason was the direct refusal of a designated respondent to participate.

Diagnosis was based on the NIMH Diagnostic Interview Schedule (DIS) (6), a highly structured interview designed for use by lay interviewers in epidemiologic studies. The DIS assesses the elements of a psychiatric diagnosis, including the presence of symptoms and their severity and frequency. Symptoms di-

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TABLE 1. Number of Subjects at Each Site and Lifetime Rates of Dysthymia According to Age and Sex in Five U.S. Sites

Age (years)	New Haven		Baltimore		St. Louis		Piedmont		Los Angeles		All Sites	
	Total N	%	Total N	%	Total N	%	Total N	%	Total N	%	Total N	%
Men[a]												
18-44	719	3.2	654	1.0	690	2.6	705	1.3	1,023	3.6	3,791	2.3
45-64	339	2.2	294	1.8	283	1.8	415	0.9	298	2.7	1,629	1.9
65 and older	995	1.4	329	0.6	208	0.5	385	0.3	154	2.5	2,071	1.0
Women[a]												
18-44	935	4.3	1,037	3.2	1,006	5.2	892	2.9	1,061	4.8	4,931	4.0
45-64	461	3.1	520	3.5	432	8.0	640	4.4	348	7.2	2,401	4.8
65 and older	1,562	3.1	499	1.3	351	1.6	788	2.5	225	2.4	3,425	2.3
Total	5,011	3.2	3,333	2.1	2,970	3.8	3,825	2.2	3,109	4.2	18,248	3.1
SE		0.18		0.14		0.19		0.15		0.20		0.17

[a]The ratio of women to men was 1.5 in New Haven, 2.5 in Baltimore, 2.6 in St. Louis, 3.0 in Piedmont, and 1.6 in Los Angeles.

rectly attributable to physical illness and alcohol or other drug intake are excluded. Computer algorithms use DIS data to generate diagnoses of the more prevalent *DSM-III* disorders: agoraphobia or simple phobia, alcohol abuse and/or dependence, drug abuse and/or dependence, major depression, bipolar disorder, dysthymia, obsessive-compulsive disorder, panic disorder, schizophrenia, schizophreniform disorder, antisocial personality disorder, somatization disorder, and anorexia nervosa. Dysthymia, as assessed by the DIS, is defined as depressed mood lasting 2 years or more, the presence of symptoms from at least three symptom groups defined by *DSM-III*, and the absence of psychotic features. Because of the exclusion of psychotic symptoms, by definition there cannot be comorbidity of dysthymia with schizophrenia or schizophreniform disorder.

The DIS also asks respondents about their use of health and mental health services in the 6 months before the interview. In addition, respondents in the New Haven study were asked about their use of psychotropic medications during this period. The sociodemographic variables used in this analysis included sex, age (18–44 years, 45–64 years, or 65 years and older), race (white or not white), current marital status (married or not married), education (four levels), household income (five levels), and current full-time employment (yes or no).

To compensate for the effects of the sampling design and nonresponse, a poststratification weight (7), based on the U.S. census population count within age, sex, and race categories for each of the five sites, was applied. The resulting final weights produced sample estimates that correspond precisely to the U.S. census count for each community. Since conventional statistical procedures assume simple random sampling and are not appropriate for analysis of complex weighted samples (8, 9), we incorporated estimates of design effects into all statistical tests presented in this report by means of Taylor Series linearization procedures produced by the SURREGR program (9–11).

Our analysis used weighted least squares procedures to compare rates of dysthymia across subgroups. Because independent samples were collected at the five sites, we first present the overall as well as the age- and sex-specific rates of dysthymia, stratified by Epidemiologic Catchment Area site. Unless otherwise noted in the test, rates of dysthymia in subsequent analyses were aggregated across the five sites only when we determined that there was no statistically significant interaction between a risk factor and a site. Tests of statistical significance were controlled for the main effect of site.

RESULTS

The mean lifetime rate of dysthymia for all five sites was 3.1% (table 1). The rates of dysthymia differed significantly among the five sites ($\chi^2=38.88$, df=4, $p<0.001$). The rate was highest in Los Angeles (4.2%) and lowest in Baltimore (2.1%).

The lifetime rates of dysthymia were higher for women at all five sites. The ratio of women to men ranged from 1.5 in New Haven to 3.0 in Piedmont. The rates were highest in the 18–64 age group and declined at age 65 and older. However, there was a significant Sex by Age interaction ($\chi^2=5.96$, df=2, $p<0.05$), indicating that the effect of sex depended on age. The difference between the rates of lifetime dysthymia for men and for women was greatest in the group that was 45–64 years old.

When we controlled for the variation in rates of dysthymia across the five sites and the interaction between sex and age, we found that only some of the other social risk factors were significantly related to the rates of dysthymia. There was no association between dysthymia and race ($\chi^2=1.52$, df=1, n.s.), education ($\chi^2=3.96$, df=2, n.s.), and current full-time employment ($\chi^2=1.86$, df=1, n.s.). However, there were significant interactions between marital status and age ($\chi^2=7.26$, df=2, $p<0.05$) and between household income and age ($\chi^2=19.44$, df=7, $p<0.01$). Table 2 presents the rates of dysthymia (adjusted for sex and

TABLE 2. Age-Adjusted Lifetime Rates[a] of Dysthymia According to Marital Status and Household Income in Five U.S. Sites

Age (years)	Percent Currently Unmarried	Percent Currently Married	Percent With Income of <$20,000	Percent With Income of $20,000 or More
18-44 (N=8,722)	3.8	2.7	4.7	2.8
45-64 (N=4,030)	5.5	2.7	3.6	4.0
65 and older (N=5,496)	1.7	1.7	2.3	2.4

[a]Rates adjusted for study site and sex. Adjusted rates reflect statistically significant interactions between age and marital status and age and household income.

site) stratified by age for marital status and income. Adjusted lifetime rates of dysthymia were higher among the unmarried than the married adults under age 65. The difference was greatest in the group that was 45–64 years old. For the youngest age group (18–44 years), rates of dysthymia were significantly greater among respondents in all groups with incomes of less than $20,000 per year than in higher income groups, although there was no effect of household income for older individuals.

As can be seen in table 3, the comorbidity of dysthymia with other disorders was very high and was statistically significant for each disorder except bipolar disorder ($\chi^2=10.83$, df=1, $p<0.001$). More than 75% of the patients with dysthymia had other disorders, particularly major depression, anxiety disorders, and substance abuse. However, among the five sites, the relationships of dysthymia to major depression and bipolar disorder varied. Rates of major depression were significantly higher among dysthymic respondents than among those without dysthymia at all of the five sites, although the magnitude of this difference was greater in Los Angeles (48.6% versus 3.7%), New Haven (43.7% versus 4.5%), and St. Louis (40.5% versus 3.0%) than in Baltimore (20.2% versus 2.6%) or Piedmont (29.2% versus 3.0%). Rates of bipolar disorder were significantly higher among respondents with dysthymia than among those without dysthymia in New Haven only (4.7% versus 1.0%; $\chi^2=3.91$, df=1, $p<0.05$). In Baltimore, only persons without dysthymia had bipolar disorder (0.3% versus 0.0%; $\chi^2=15.76$, df=1, $p<0.001$). The comorbidity of dysthymia was highest with major depression (odds ratio=16.61), followed by panic disorder (odds ratio=8.33), and any disorder (odds ratio=8.32).

When differences in study sites were controlled for, persons with dysthymia were significantly more likely than others to report recent (6-month) contact with general health services and mental health treatment services in both general medical and specialty settings (table 4). The difference was greatest in the use of specialty mental health services: persons with dysthymia were almost five times more likely than those without dysthymia to have received treatment within 6 months of their interviews. Among New Haven residents, for whom data on use of psychotropic medication were available, dysthymia was associated with use of many types of psychotropic medication as well. Dysthymic persons reported significantly greater use of minor tranquilizers, antidepressants or lithium, and sedatives. There was no difference in use of major tranquilizers ($\chi^2=0.13$, df=1, n.s.) or stimulants ($\chi^2=1.97$, df=1, n.s.) among persons with and without dysthymia.

DISCUSSION

According to the data from this study, dysthymia is a highly prevalent disorder, particularly among women under 65 years of age, unmarried persons, and young persons with low income. It is associated with greater use of general health and psychiatric services and of psychotropic drugs, especially minor tranquilizers, antidepressants, and sleeping pills. It has high comorbidity with other psychiatric disorders, particularly major depression, anxiety disorders, and substance abuse. The fact that only 25%–30% of cases occur in the absence of other psychiatric disorders (pure dysthymia) raises questions about its uniqueness as a specific disorder. Persons with "pure dysthymia" may have early symptoms of another disorder, or they may have symptoms associated with medical disorders.

There are no other published community survey rates of dysthymia as defined by *DSM-III* criteria. A 1975 New Haven survey (12) based on the Research Diagnostic Criteria included depressive personality, a diagnosis quite close to dysthymia. The lifetime rate of dysthymia in that survey was 4.5%, which is somewhat higher than the range of lifetime rates, 2.1%–4.2%, reported in the five Epidemiologic Catchment Area sites. Unlike the data from the Epidemiologic Catchment Area, there were no sex differences in the rates of depressive personality in the 1975 New Haven survey. However, like the rates in the Epidemiologic Catchment Area study, the rates diminished in persons 65 years of age and older.

The data from the Epidemiologic Catchment Area on bipolar disorder and major depression suggest that the onset and highest risk periods for major depression and bipolar disorder are in young adulthood and that a residual group of persons have dysthymia in middle and old age (13). Major depression seems to be more commonly a disorder of women between the ages of 18 and 44, whereas dysthymia, a chronic condition, is highly prevalent in women up to age 64.

Consistent with the Epidemiologic Catchment Area data, there is strong evidence from family (14–16) and clinical (17, 18) studies that major depression and dysthymia are overlapping disorders. Major depression and dysthymia, termed "double depression," co-occur in approximately 40% of individuals seeking treat-

TABLE 3. Rates of Other Disorders in Persons With and Without Dysthymia and Odds Ratios of Comorbidity With Dysthymia in Five U.S. Sites (N=18,572)

Other Psychiatric Disorder	Percent With Other Disorder: Persons With Dysthymia	Percent With Other Disorder: Persons Without Dysthymia	χ^2 (df=1)[a]	p	Odds Ratio[b]
Major depression	38.9	3.4	799.6	<0.001	16.61
Panic disorder	10.5	1.2	181.5	<0.001	8.33
Any anxiety disorder	46.2	15.2	300.7	<0.001	4.70
Bipolar disorder	2.9	0.7	24.9	n.s.	3.90
Substance abuse	29.8	15.4	125.9	<0.001	3.20
Any DIS/*DSM-III* disorder	77.1	30.5	423.1	<0.001	8.32

[a]Significance tests were controlled for differences across sites. Rates were higher for bipolar disorder only at New Haven and Baltimore.
[b]Adjusted for study site, age by sex.

TABLE 4. Treatment Services Used by Persons With and Without Dysthymia and Odds Ratios of Utilization With Dysthymia in Five U.S. Sites (N=18,572)

Treatment	Percent Using Treatment: Persons With Dysthymia	Percent Using Treatment: Persons Without Dysthymia	χ^2 (df=1)	p	Odds Ratio[a]
Any health service	67.9	54.3	32.61	<0.001	1.77
Mental health treatment					
In a general medical setting	11.5	3.8	28.06	<0.001	3.19
In a specialty setting	15.0	3.1	47.89	<0.001	5.21
Psychotropic medication[b]	27.3	10.5	39.90	<0.001	3.28
Minor tranquilizers	19.0	7.4	9.71	<0.01	2.91
Major tranquilizers	1.0	0.8	0.13	n.s.	1.31
Antidepressants or lithium	6.4	1.3	6.46	<0.05	5.09
Sedatives	6.7	2.7	4.76	<0.05	2.87
Stimulants or other	4.9	0.8	1.97	n.s.	6.03

[a]Adjusted for study site, age by sex.
[b]Medication use reported for New Haven site only (N=5,034).

ment for depression. Family studies indicate a greater risk of dysthymia in the first-degree relatives of probands with major depression. Follow-up studies report that many patients with major depression later become dysthymic (14, 19). While the association between these disorders is well established, the mechanism of the association is unclear. Dysthymia may be a mild manifestation of major depression, or it may be the consequence of untreated or only partially resolved episodes of major depression that have become chronic (15).

The finding of an age difference in the peak prevalence rates of major depression and dysthymia is interesting because it suggests that dysthymia may be a residual state that follows major depression. Since the onset of major depression occurs most commonly when people are in their late 20s, the high rates in the younger age groups may be a reflection of new onset. The dysthymia that remains in the older age groups may be the residual disorder following untreated major depression or partial recovery from major depression. Since we cannot assess the onset of dysthymia on the basis of the present data, we cannot determine whether older women who report dysthymia have had episodes of untreated major depression before their dysthymia.

In summary, the epidemiologic findings on the age- and sex-specific prevalence rates and comorbidity of dysthymia were reasonably consistent across geographic areas in the United States and were reasonably consistent with findings reported from clinical studies. These findings also suggest that the onset and highest risk periods for other affective disorders are in young adulthood, with a residual state of dysthymia in middle and old age. Questions about the uniqueness of dysthymia as a distinct disorder remain.

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Ventricular and Sulcal Size at the Onset of Psychosis

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To determine whether abnormalities in brain morphology are present at the onset of illness, patients with schizophrenia, schizophreniform and bipolar disorders, and major depression who were experiencing their first episodes of psychosis were compared with normal and medical control subjects. The schizophrenic patients had larger third ventricles but not larger lateral ventricles or cortical sulci than the normal subjects. The other psychotic patients did not differ from the normal group on these measures. A different pattern of results emerged when the medical patients were used for comparison, indicating that the choice of control group can influence the findings of computerized tomography studies.

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An important issue in computerized tomography (CT) studies of functional psychosis is, When in the course of illness do structural anomalies appear in the brain? If they predate or are present at the onset of a disorder, they may have etiological significance and could serve as indexes of underlying vulnerability. If they appear sometime after the onset of illness, they may result from the progression of the disorder or the cumulative effects of somatic treatments. The vast majority of CT investigations have focused on patients with a history of psychopathology. The few studies that have examined cerebral morphology at the onset of illness have been limited to subjects with schizophrenic and schizophreniform psychoses and have focused on lateral ventricle enlargement.

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Weinberger et al. (1) found that 20% of a group of 35 patients with schizophreniform disorder had enlarged lateral ventricles; they also noted that 14% of this group had a higher than normal rating on a scale that measured cortical atrophy. Schulz et al. (2) subsequently examined 15 teenage patients with schizophrenia or schizophreniform disorder during their first episodes and found that 53% had ventricular enlargement. However, in one study (3) ventriculomegaly was found in old but not young schizophrenic subjects, and two well-controlled investigations of schizophrenic patients (4, 5) failed to identify lateral ventricle enlargement, thus challenging the general nature of this phenomenon.

These conflicting findings are subject to various interpretations. It is possible that only a select group of patients have ventricular enlargement and that these individuals have been sampled to varying degrees in different clinical settings. Another possibility is that control subjects differ in important ways across research settings. In a meta-analysis of CT studies of schizophrenia, Smith and Iacono (6) found that studies reporting positive versus negative findings showed differences not in the ventricle sizes of the schizophrenic patients but in the ventricle sizes of the control subjects: studies reporting enlargement in schizophrenic subjects had used control subjects with small ventricles, and investigations failing to demonstrate greater ventricular size in schizophrenic patients had used control subjects with large ventricles. Smith and Iacono (6) also found that control groups composed of medical patients had smaller ventricles than control groups composed of normal volunteers.

The purpose of the present study was to extend this research along several important lines. We developed an extensive, community-based referral network that allowed us to sample a broader range and a more representative sample of psychotic patients than has been studied before. In addition to patients with schizophrenic and schizophreniform disorders, those with bipolar disorder and major depression were included. To our knowledge, this investigation was the first to examine these types of patients, all of whom had psychotic symptoms, during their first lifetime episodes. Unlike our predecessors, we included two nonpsychiatric comparison groups (a community-based sample of normal volunteers and a group of medical pa-

tients), thus making it possible to evaluate more directly how the choice of control group affects the outcome of a CT study. Finally, we examined concurrently the three cerebral structures (lateral ventricles, third ventricle, and cortical sulci) most commonly studied in psychiatric patients.

METHOD

Subjects

Eighty-five individuals who were experiencing their first lifetime episodes of psychosis served as subjects. These patients were recruited within 3 months after treatment for their psychoses began. For all but 10 of these individuals, this treatment included hospitalization. Our operational definition of first episode included only subjects 1) who were currently psychotic (i.e., experiencing hallucinations or delusions, displaying grossly disorganized behavior, showing marked thought and speech disorder, or having two of the following symptoms: marked loss of drive, social withdrawal, severe excitement, overwhelming anxiety or fear, and gross self-neglect) and 2) who had not been treated before the present episode with antipsychotic, antimanic, or antidepressant drugs. Other inclusion and exclusion criteria required 1) that subjects have lived in the Vancouver metropolitan area for at least 6 months, 2) that they be between 15 and 54 years of age, and 3) that they not have an organic cerebral illness, severe mental retardation, a chronic physical disorder, or chemical dependence. Potential subjects, including doubtful and borderline cases, were initially recruited for the study and then their final disposition was decided by the results of a thorough clinical investigation that included administration of the Present State Examination (7), review of clinical charts, and interviews with family members and friends.

In an attempt to minimize selection bias, a community-wide network of referral agencies was established. This included all psychiatric hospitals and psychiatric services of general hospitals in the metropolitan area, university and college counseling services, community mental health centers, psychiatrists in private practice, private counseling services, employment and immigration counseling services, and a random sample consisting of one-sixth of the general practitioners in Vancouver. Every psychotic person who was identified during the 2 years that subjects were recruited and who gave informed consent was considered as a potential subject for the study.

Diagnoses were made according to *DSM-III* criteria. The clinical material was reviewed at a case conference that was attended by the project staff and that always included at least two experienced diagnosticians (psychiatrists and clinical psychologists). Each criterion specified for each possible diagnosis of a functional psychosis (i.e., the *DSM-III* categories of schizophrenic disorders, paranoid disorders, affective disorders, and psychotic disorders not elsewhere classified) was reviewed to determine whether it was met or not met by a potential subject. Then the clinical algorithms supplied in *DSM-III* were strictly followed to arrive at a diagnosis. Diagnoses were made without access to CT scan data. Only subjects who met the *DSM-III* criteria for an active schizophrenic, schizophreniform, or major affective disorder (with psychotic features) were retained for study. The characteristics of these 85 psychiatric patients, including their sex, age, and *DSM-III* diagnosis, are presented in table 1.

The normal control group consisted of 44 Vancouver residents with no personal history of mental disorder, chronic physical illness, or chemical abuse. In addition, these individuals had no family history of psychiatric disorder and did not qualify for any psychiatric diagnosis on the basis of an interview with an abbreviated version of the Diagnostic Interview Schedule (8). These normal control subjects were recruited by posters and brochures placed at family practice units, employment centers, and community centers. Volunteers who did not meet the exclusion criteria, who were between the ages of 15 and 54, and who had lived in the metropolitan area for 6 months or longer served as control subjects.

The medical control group (N=30) included all age-appropriate medical patients who received CT scans in a 3-month period that overlapped the interval during which the psychiatric patients and normal control subjects were given CT scans. For a medical patient to be selected, the radiologist's report had to indicate that there was no pathology. Interpretive comments indicating that the ventricles were unusually large for the subject's age did not disqualify a patient from inclusion in this group (three such individuals were included). The CT scans were not viewed by members of the research team before these selections were made. The reasons given for these patients' referrals for CT scans were to investigate headaches (N=12), to rule out space-occupying lesions (N=9) and multiple sclerosis (N=4), to investigate suspected seizure disorders (N=3) and intracerebral calcification (N=1), and to assess postinjury head trauma (N=1). The age and sex of the subjects in the two control groups can be seen in table 1.

Apparatus and Procedure

All CT scans were performed using the same third-generation, high-resolution (256×256), total-body scanner (Seimens Somatom DR2). The window width was set at 80 and the level at 27. From 13 to 16 serial cross-sections of the brain, 8 mm in thickness, were scanned parallel to the canthomeatal line. The CT scan that showed the lateral ventricles at their largest was enlarged (using the digital data) to 60% of life size. This procedure allows more accurate tracing of the ventricle margins than is possible from small images and substantially lessens the error variance associated

TABLE 1. Sex and Age of 85 Psychotic Patients and 74 Control Subjects in a Study of Ventricular and Sulcal Size

Group	Number of Subjects			Age (years)		
	Male	Female	Total	Mean	SD	Range
Psychotic patients	63	22	85	23.5	6.5	15–43
Schizophrenia	26	5	31	22.8	5.7	15–37
Schizophreniform disorder	17	3	20	20.6	4.4	16–33
Bipolar disorder	9	9	18	26.1	7.6	18–43
Major depression	11	5	16	22.6	4.0	17–30
Medical control	13	17	30	22.9	4.4	15–32
Normal control	29	15	44	23.2	5.6	15–42

with measuring very small areas with a planimeter. A Sokkish 19908 compensating polar planimeter was used to measure the area of the lateral ventricles and the area of the brain. Measures were taken while the CT scan was affixed to a horizontal white translucent table that was illuminated from below.

Third ventricle measurements were made with a traveling microscope (Precision Tool and Instrument Co., type 2160). This microscope can be moved through x, y, and z axes by means of adjustment screws. The magnitude of each movement is given on a vernier scale calibrated to 0.001 mm. The microscope has cross hairs on the lens to allow accurate positioning of the instrument along each side of the third ventricle. The frame that holds the microscope is mounted on a white translucent plastic table that is illuminated from below.

A uniform CT scanning procedure was performed for all subjects. A molded headrest was used to stabilize the head of each participant while the CT scan was made. All psychiatric and normal control subjects gave informed consent for their participation in the study.

All measures were taken from the CT scans without knowledge of the subjects' identities or group membership. The planimeter was used to trace the area of each of the lateral ventricles three times and the area of the brain six times. The mean of the three measures was calculated for each ventricle. These mean values were added together and divided by the mean of the six measures of the brain. This ratio was multiplied by 100 to give the ventricle-brain ratio (VBR) as it has been reported in most previous studies.

The CT slice that showed the third ventricle at its largest was fixed to the illuminated table of the traveling microscope while the microscope was positioned and measurements were taken. The width of the third ventricle was measured at the widest point at which a continuous ventricle wall could be seen. The measurements, which were in millimeters, were converted to life size by multiplying by a constant.

Unlike measures of the third and lateral ventricles, no consensus has been reached about how cortical atrophy should be assessed. Measures of specific sulci have been used by some investigators (3), while others have used global ratings (1, 5). We chose the latter approach and made a rating of cortical atrophy on a 3-point scale. A rating of 1 indicated that no sulci were visible, 2 indicated that some sulci were visible but not extensive, and 3 was used to indicate scans in which visible sulci were extensive. To standardize the choice of scan for making these ratings, we used the CT scan three slices above the scan that showed the lateral ventricles at their largest. This scan was matched to a sample of nine scans (three for each rating) that showed the variability allowed by each of the three rating scores.

RESULTS

Intraclass correlations between the measurements of two independent raters indicated high measurement reliability for the size of the lateral ventricles (ICC= 0.92, $p<0.001$, based on 30 cases selected at random) and the third ventricle (ICC=0.97, $p<0.001$, based on 20 cases selected at random). There was complete agreement between two independent judges on 90% of the ratings of cortical atrophy. Discrepancies in ratings were resolved through discussion and mutual agreement. No CT measure was significantly correlated with age for any subject group. There were more men than women in all groups except the bipolar disorder and medical control groups. However, t tests of sex differences on each CT measure (lateral ventricles, third ventricle, and cortical sulci) for the psychotic patients, normal control subjects, and medical control patients failed to reach significance (for the nine t statistics calculated, all p values were greater than 0.10). The data for men and women were therefore combined for all further comparisons.

To examine group differences, a one-way analysis of variance (ANOVA) was calculated for each CT measure (lateral ventricles, third ventricle, and cortical sulci) over the six subject groups (schizophrenia, schizophreniform disorder, major depression, bipolar disorder, normal control, and medical control). To achieve an error rate of 0.05 overall, the alpha level of each of the three ANOVAs was adjusted by means of the Bonferroni correction procedure to 0.017. Planned orthogonal contrasts, with the significance level set at 0.05, were used to determine whether the psychiatric patients showed more dilation than each of the control groups and whether the normal control subjects had larger ventricular and sulcal spaces than the medical patients.

The mean size and distribution of the lateral ventricles were very similar across groups (table 2). No significant group differences were found ($F=0.51$, $df=5$, 153, $p>0.10$). If the normal control group's mean VBR plus two standard deviations is used to define ventricular enlargement, one (3%) of the schizophrenic patients and two (5%) of the normal control subjects had enlarged ventricles. If the medical control group's mean VBR plus two standard deviations is used as the standard, three (10%) of the schizophrenic,

TABLE 2. Ventricular and Sulcal Size in 85 Psychotic Patients and 74 Control Subjects

Group	Ventricle-Brain Ratio		Third Ventricle Width (mm)		Sulcal Dilation[a]	
	Mean	SD	Mean	SD	Mean	SD
Psychotic patients						
Schizophrenia	6.74	2.59	4.05[b]	1.55	2.06	0.85
Schizophreniform disorder	5.92	2.38	3.28	0.84	1.95	0.76
Bipolar disorder	6.20	1.95	3.33	1.01	1.89	0.83
Major depression	6.36	2.96	3.63	0.88	2.00	0.89
Medical control	5.77	2.55	3.01[c]	0.90	1.39	0.61
Normal control	6.39	2.76	3.49	1.13	1.82	0.76

[a]Rating on a 3-point scale; higher scores indicate greater sulcal width.
[b]Significantly different from the normal control group ($t=1.81$, $df=73$, $p<0.05$).
[c]Significantly different from the normal control group ($t=1.94$, $df=72$, $p<0.05$).

one (5%) of the schizophreniform disorder, and one (3%) of the medical patients had enlarged ventricles.

A one-way ANOVA across subject groups for third ventricle width showed a significant difference ($F=2.97$, $df=5, 153$, $p<0.017$). However, the Bartlett test (9) for the homogeneity of variance indicated that group variances were heterogeneous ($\chi^2=14.49$, $df=5$, $p<0.05$). The presence of unequal variances violates an assumption of ANOVA and, with unequal numbers of subjects in the groups, can seriously affect the alpha level that is obtained. A moderately strong positive Spearman correlation (0.66) between group size and variance indicated that large variances tended to be associated with large groups. Under these circumstances, the alpha level is likely to be underestimated by the ANOVA (10); the null hypothesis of no group differences in third ventricle size was therefore rejected.

Planned orthogonal contrasts with the measurements of the normal control subjects indicated that third ventricles were larger in the schizophrenic patients than in the normal control subjects and smaller in the medical patients than in the normal control subjects (table 2). When we used the normal control group's mean VBR plus two standard deviations to define third ventricle enlargement, three (10%) of the schizophrenic patients and two (5%) of the normal control subjects had enlargement. Comparison of the medical control group with the psychiatric groups revealed that the width of the third ventricle was greater in the schizophrenic and depressed patients than in the medical patients. If the measurements of the medical patients are used as a basis for defining normal third ventricle size, eight (26%) of the patients with schizophrenia, one (5%) with schizophreniform disorder, one (6%) with bipolar disorder, one (6%) with major depression, and one (3%) of the medical patients had enlargement of the third ventricle.

The size and distribution of cortical atrophy ratings were similar across all groups except for the medical control group (table 2). A one-way ANOVA indicated a significant group effect ($F=2.95$, $df=5, 153$, $p<0.017$). Planned contrasts indicated only that the medical group differed significantly from all the other groups.

Correlations were computed between each possible pairing of two CT measures for each group. The patterns of correlations within the psychiatric patient groups were similar, as were the patterns in the two control groups, so average correlations were computed separately for the combined groups of psychiatric and control subjects. For the 85 psychotic subjects, the correlations were 0.24 ($p<0.05$), 0.16, and 0.02, respectively, for VBR versus third ventricle width, third ventricle width versus cortical atrophy rating, and VBR versus cortical atrophy rating. The corresponding correlations for the 74 control subjects were 0.48 ($p<0.05$), 0.25 ($p<0.05$), and 0.14 (one-tailed tests). The correlation between VBR and third ventricle width was significantly larger ($p<0.05$, one-tailed) for the control subjects than for the psychotic subjects.

DISCUSSION

The results indicate that near the time when psychotic symptoms appeared in the broad-based sample of psychiatric patients in our study, third ventricle enlargement was present in the schizophrenic patients but not in the other psychotic subgroups we examined. Although our investigation is the first, as far as we know, to examine the third ventricle during the first episode of psychosis, our results are consistent with those of many other studies that have described dilation of this structure in chronic schizophrenic patients (see 5, 11–13). Recently, Houston et al. (14) reported a correlation of −0.90 between third ventricle width and CSF homovanillic acid concentration in chronic schizophrenic patients. This finding, together with the various reports of third ventricle enlargement in schizophrenia, suggests that atrophy of dopaminergic neural structures lateral to the third ventricle may account for increased ventricular width in schizophrenic patients.

To our knowledge, third ventricle size in patients with major affective disorders has not been assessed in other CT investigations. Hence, further studies of groups of chronic patients with psychotic bipolar disorder and major depression are needed to determine whether changes in the third ventricle arise with the progression of these disorders.

Our findings are consistent with the possibility that third ventricle enlargement was present before the onset of illness in the schizophrenic patients. However, the absence of ventricular enlargement in the schizophreniform disorder patients argues against such an interpretation unless different biological mechanisms are involved in the etiology of these disorders. In the present study, the primary difference between these two groups was that the schizophrenic patients were more likely to have had an insidious onset and a his-

tory of prodromal symptoms. If schizophrenia and schizophreniform psychosis are variants of the same disorder, it may be that enlargement of the third ventricle appears some number of months after the first appearance of prodromal or psychotic symptoms. Thus, schizophrenic patients, because they have been ill longer, would be more likely than those with schizophreniform disorder to show third ventricle widening. This hypothesis could be tested by giving repeat CT scans to patients with schizophreniform disorder who are later diagnosed as having schizophrenia.

Although the schizophrenic patients had the largest lateral ventricles, lateral ventricle size did not differentiate the psychiatric patient groups from the control groups. The failure to find a significant effect was not due to a lack of statistical power. The effect size reported by Weinberger et al. (1) was 0.7 standard deviations. The power for detecting a similar effect size in the schizophrenic group in the present study was high—about 95%. Moreover, the absence of a significant difference was not attributable to the choice of control group; neither the normal nor the medical control group differed from the psychotic patient groups. Our data are consistent with those of other investigators who have found third but not lateral ventricle enlargement in chronic schizophrenic patients (5, 11–13). Interestingly, the correlation between lateral and third ventricle size was significantly smaller for all the psychotic patients than for the normal and medical control subjects combined. This result suggests that the factors which determine the size of these structures in psychotic patients are different from those operating in nonpsychotic individuals.

Our findings, as well as those of other investigators who have failed to demonstrate lateral ventricle enlargement in chronic schizophrenic subjects, are difficult to reconcile with those indicating enlargement of the lateral ventricles in first-episode schizophrenic and schizophreniform disorder patients (1, 2). Although various procedural factors could account for these discrepant results, it is possible that a subset of patients with schizophrenia, those most severely afflicted with this disorder, have been tapped in the studies reporting positive results (2). Unfortunately, there is no currently accepted index of severity, so it is difficult to evaluate this notion.

Dilation of the cortical sulci was not evident in any patient group when compared to the normal control subjects. This result suggests that if atrophy is present in psychotic patients, it probably occurs well after the onset of psychosis. However, because few medical control patients had any visible sulci, all other groups appeared to have cortical atrophy when compared with this control group, suggesting that use of such control subjects may bias the results of CT studies. Indeed, if the measurements of the medical patients are used as the standard of normal brain morphology, then the patients with major depression, in addition to the schizophrenic patients, had enlargement of the third ventricle ($t=2.23$, $df=44$, $p<0.05$), and the difference in lateral ventricle size approaches significance ($t=1.47$, $df=59$, $p<0.10$) when the schizophrenic and medical control groups are compared. In addition, the medical control patients had significantly smaller third ventricles and sulci than the normal control subjects. It is not clear what factors were responsible for this medical patient bias, but it may be that medical patients with normal but large ventricles and/or sulci were excluded from the study, and patients whose pathology decreases the size of the fluid spaces were included.

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The Revision of Axis V in *DSM-III-R*: Should Symptoms Have Been Included?

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The authors studied the relationship of psychological symptoms to clinicians' ratings on DSM-III's *axis V. A total of 355 patients received multiaxial assessments and were reinterviewed under blind conditions with the Psychiatric Epidemiology Research Interview, which contains scales to measure aspects of social and occupational functioning and various symptom dimensions. The majority of symptom scales were correlated significantly with axis V ratings. Axis I diagnosis explained 19.0% of the variance in axis V; demographics, 6.5%; and symptoms, 7%. Symptoms had a larger effect, in terms of explained variance, than adaptive functioning variables and tended to detract from the latter's significance. These results have implications for axis V in* DSM-III-R *and for planning* DSM-IV.

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In spite of a reputation as a major advance in the classification of mental disorders (1–4), the *DSM-III* multiaxial evaluation system has failed to achieve widespread clinical use or to generate significant research. *DSM-III* axis V (highest level of adaptive functioning in the past year) has been the subject of only a handful of empirical studies (5–11). As a result, the Multiaxial Advisory Committee to the APA Work Group to Revise *DSM-III* has revised axis V to explicitly include symptoms, as well as indicators of social and occupational functioning, in the rating. Axis V in *DSM-III-R*, therefore, has been transformed into a hybrid version of the Global Assessment Scale (GAS) (12) and the Children's Global Assessment Scale (13) and has been renamed the Global Assessment of Functioning Scale. Since the GAS has proven valuable in research and is widely used, the revised axis V is expected to be more utilized and more useful.

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There have been no studies, however, to assess the potential impact of this change on the multiaxial system. In a previous study (14), we found that several aspects of occupational and social functioning determined clinicians' ratings on axis V, independently of axis I diagnosis and demographic variables. Thus, in keeping with the intent of multiaxial diagnosis (15), axis V ratings provided information about patients that was distinct from standard diagnostic categories and added, therefore, to a more comprehensive clinical description of patients with mental disorders (16). In this study, we investigate the relationship of symptoms to axis V ratings, independent of diagnostic status, and the effect of including symptom ratings on the social and occupational variables that we have shown to be significantly related to axis V. Our study sheds light on the likely consequences of the revision of axis V in *DSM-III-R*.

METHOD

A total of 362 subjects were recruited from the Vanderbilt Psychiatric Outpatient Clinic of the Presbyterian Hospital (N=300) and the inpatient unit of the Washington Heights Community Service in the New York State Psychiatric Institute (N=62). Informed consent was obtained after the procedures were explained to the subjects. All subjects had complete *DSM-III* multiaxial evaluations by psychiatric residents, psychology interns, and medical student/psychiatric attending pairs who staff the clinical services. All trainees and supervisors had considerable training in the use of *DSM-III* as part of their regular educational programs or through special *DSM-III* courses taught by the senior author. The senior author and the other senior members of the Biometrics Research Department of the New York State Psychiatric Institute also independently checked the assessments of every subject by direct supervision of the trainees or against chart information to ensure that errors were identified and corrected (17).

The diagnostic distribution of the patients was heterogeneous. By *DSM-III* criteria, 64 patients had schizophrenia; 35, other nonaffective psychotic disorders; 118, major depression; 27, other depressive disorders; 23, anxiety disorders; 24, adjustment disor-

ders; 35, other nonpsychotic disorders; and 24, V codes or no axis I diagnosis. Five patients had diagnoses deferred on axis I. For the purposes of the analyses reported here, we divided the major depressive disorders into first episode (N=59) and recurrent (N=59) and collapsed all other nonpsychotic disorders and other codes in a broad "other diagnoses" category (N=138). Seven patients who had no axis V rating were excluded from the analyses.

With respect to demographic characteristics, the sample was also heterogeneous. Axis V ratings were obtained for 125 men and 230 women. A total of 135 subjects were 18–29 years old, 98 were 30–39, 68 were 40–49, and 54 were over 50 years old. Eighty-one subjects were married, 114 were separated or divorced, 124 had never married, 20 were widowed, and 15 were other (this last group consisted of patients who volunteered that they were homosexual and in various living arrangements) (N=354 for marital status due to one missing value). A total of 109 subjects were Hispanic, 104 were black, 129 were white, and 13 belonged to other racial groups. Forty-eight patients had less than an eighth-grade education, 80 had not graduated from high school, 86 had at least graduated from high school, 72 had some college education, and 69 were college graduates.

All subjects were interviewed independently, within 6 months of their clinical evaluations, by a field staff of trained interviewers who administered the Psychiatric Epidemiology Research Interview, which contains a series of scales designed to measure various aspects of social and occupational functioning (18) as well as various dimensions of psychiatric symptoms (19). The time period investigated with this interview was either the 1-year period or the 1-month period preceding the subject's index clinical evaluation. Since we have found (14) few differences in the effects of adaptive functioning variables on axis V ratings between the two time periods, the data have been combined in this report. All interviews were conducted by interviewers who were blind to the patients' multiaxial diagnostic evaluations.

The patients rated themselves on a variety of symptom scales included in the Psychiatric Epidemiology Research Interview. These scales, ranging in length from three to 27 items, have been used in epidemiologic surveys and have been shown to be reliable and useful in screening for cases of psychiatric disorder in the general population (19). The scales used in this study measured the following symptom dimensions: active expression of hostility (10 items), false beliefs and perceptions (13 items), demoralization (27 items), problems due to drinking (five items), reasons for drinking (6 items), enervation (seven items), insomnia (three items), somatic problems (nine items), and sexual problems (three items). The active expression of hostility scale included items measuring how often, when the person was angry, he or she swore or cursed, got into an argument, yelled or shouted, made threatening gestures, acted violently toward objects, hit someone, hid anger, calmly explained feelings, or avoided arguing (the last three items are scored in the opposite direction from the first six). The reasons for drinking scale asked how important drinking was to the person as a means of forgetting everything, forgetting worries, relieving tension and nervousness, cheering up from a bad mood, relaxing, or just getting through the day. The sexual problems scale measured lack of interest in sex, lack of pleasure from sex, and inhibited orgasm. All scale questions were rated on a 5-point severity scale; 0=never having the symptom, 1=almost never, 2=sometimes, 3=fairly often, and 4=very often experiencing the symptoms.

The functioning measures that we found, by means of a multiple regression analysis, to be significant predictors of axis V ratings were housework neglect (seven items) and job instability (two items). Job instability describes the extent to which the person was unemployed, partially employed, or employed full-time during the previous year. The housework scale applied only to those who said they shared in doing the housework at least equally. Scale scores ranged from 0 to 4, with a score of 0 representing high functioning and 4 representing poor functioning. These scales have been previously demonstrated to have high internal consistency reliability with patients (alpha=0.85 and 0.84, respectively) and some degree of validity in terms of their ability to separate patients from nonpatients (18).

In a subset of patients with major depression and nonaffective psychoses, we found (14) that a characteristic of their social network (20), the number of people who were available to provide concrete help if needed, was a significant predictor of axis V ratings. In these same patients, level of income from wages, self-employment, or tips also significantly predicted ratings on this axis. We included these variables, "number of instrumental supporters" and "earned income," with our other two functioning variables in the present analyses.

Correlation coefficients were calculated between axis V ratings and the broad diagnostic groups, sociodemographic variables, and the nine symptom scales. A series of multiple regression analyses were performed to examine the relationship of scores on the symptom scales to axis V ratings, over and above the contributions made by diagnostic group and demographic variables. Our four social and occupational functioning variables were then added to the regression equations in order to assess the effect on their contributions to axis V ratings when symptom effects were also included.

RESULTS

The distribution of axis V ratings was as follows. One patient (0.3%) received a rating of 1–superior; 19 (5.4%), 2–very good; 82 (23.1%), 3–good; 135 (38.0%), 4–fair; 76 (21.4%), 5–poor; 35 (9.9%), 6–very poor; and seven (2.0%), 7–grossly impaired.

Table 1 presents the mean axis V ratings for each of

TABLE 1. Effect of Diagnosis on Axis V Ratings in 355 Psychiatric Patients

Diagnostic Group[a]	N	Axis V Rating Mean	Axis V Rating SD
Schizophrenia	64	5.13	1.16
Other psychotic disorders	35	4.14	1.03
Major depression, single episode	59	3.83	0.95
Major depression, recurrent	59	4.07	0.89
All other diagnoses	138	3.80	1.02

[a]One-way analysis of variance (ANOVA), sum of squares: between diagnoses=83.51, within diagnoses=357.04; F=20.47, df=4, 350, p<0.001. Diagnosis accounted for 19.0% of the total variance.

TABLE 2. Correlation of Axis V Rating With Psychiatric Epidemiology Research Interview Symptom Scores in 355 Psychiatric Patients

Symptom Scale	r	df[a]	p
Active expression of hostility	0.14	352	<0.01
False beliefs and perceptions	0.33	354	<0.001
Demoralization	0.13	354	<0.05
Problems due to drinking	0.23	351	<0.001
Reasons for drinking	0.17	347	<0.01
Enervation	0.10	354	n.s.
Insomnia	0.12	354	<0.05
Somatic problems	0.17	352	<0.01
Sexual problems	−0.02	347	n.s.

[a]The degrees of freedom differ from scale to scale due to missing values on some scales. In no case were more than seven cases (2%) missing.

five broad diagnostic categories and the corresponding analysis of variance results. Although axis V ratings differed significantly across axis I categories and 19.0% of the variation of the ratings was attributable to diagnosis, it is interesting to note that almost 80% of the variation of the ratings was within diagnostic categories and is hence unexplained by axis I. This is as it should be, since axis V is intended to capture aspects of disorder that are distinct from (unexplained by) axis I.

Table 2 shows the bivariate correlations between the nine symptom scales and the axis V ratings. Seven of these correlations were significant, and all but one were in the expected direction. Clearly, the frequency and severity of symptoms were associated with the clinicians' judgments of functioning as measured by the axis V scale.

Table 3 is a regression analysis that shows the effects of symptom scales in the context of other potential influences on axis V ratings. Diagnostic distinctions were entered first, a set of sociodemographic variables next, and symptom scales last.

We chose this order to determine whether symptoms contributed to axis V ratings over and above diagnosis and demographics. As can be seen from table 3, major diagnostic group explained 19.0% of the variance in axis V ratings, demographic variables (especially education) an additional 6.5%, and symptom scales another 7%; this brings the total variance explained to

TABLE 3. Multiple Regression Analysis Showing Impact of Diagnosis, Sociodemographic Variables, and Symptoms on Axis V Ratings in 355 Psychiatric Patients

Variable	Increment to Explained Variance (%)	Significance of Increment Due to Set of Variables Entered in Order Specified F	df	p
Step 1: axis I diagnosis[a]	19.0	20.5	4, 350	<0.001
Step 2: sociodemographic variables				
Age (years)				
Sex				
Education (years)	6.5	3.7	8, 342	<0.001
Marital status[b]				
Ethnicity[c]				
Step 3: Psychiatric Epidemiology Research Interview symptom scale scores				
Active expression of hostility				
False beliefs and perceptions				
Demoralization				
Problems due to drinking	7.0	3.8	9, 333	<0.001
Reasons for drinking				
Enervation				
Insomnia				
Somatic problems				
Sexual problems				

[a]Dummy variables to reflect schizophrenia; other psychotic disorders; major depression, first episode; major depression, recurrent; and all other diagnoses.
[b]Dummy variables to reflect married, separated/divorced, widowed, and single.
[c]Dummy variables to reflect Hispanic, black, and white.

32.5%. We also examined (not shown in table 2) the effect, at each step of the analysis, of the controls we entered on the individual symptom scales. With diagnosis controlled, each of the symptom scales, with one exception (sex problems; t=0.38, df=1, 349, p>0.05), would independently make an additional significant (p<0.01) contribution to the explained variance if entered next (t values ranged from 2.68 for insomnia to 5.00 for false beliefs and perceptions; df=1, 349 for each). With both diagnosis and demographics controlled, each symptom scale would still be significant at p<0.01 (t values ranged from 3.07 for enervation to 4.27 for false beliefs and perceptions; df=1, 341 for each), except for insomnia (t=1.98, df=1, 342, p< 0.05). When all symptom scales were entered together they exerted a joint effect, such that each alone was not significant except for active expression of hostility (t=2.14, df=1, 333, p<0.5). Symptoms, therefore, vary in a way that is independent of both diagnosis and demographics and are currently influencing clinician ratings on axis V.

Given this result, we examined the effect of symptoms on the association between the four adaptive functioning variables and axis V ratings that we had found previously. Job instability (t=3.43, df=1, 322,

$p<0.001$) and number of instrumental supporters ($t=-2.43$, $df=1, 139$, $p<0.05$) showed a slightly diminished effect on axis V ratings, income remained very significant ($t=-4.41$, $df=1, 135$, $p<0.001$), and housework neglect became nonsignificant ($t=0.28$, $df=1, 157$, $p>0.05$) when symptoms were statistically controlled in the regression equations. Thus, not only do symptoms appear to exert a larger effect on axis V in terms of explained variance than most of our adaptive functioning variables, but they tend to account for the same variance as the few functioning variables that seemed important in the axis V ratings.

DISCUSSION

The results of these analyses show that symptom ratings are significant predictors of adaptive functioning ratings over and above psychiatric diagnosis, which already accounts for the largest proportion of explained variance on axis V. Compared with social and occupational functioning measures, correlations of symptom scales and axis V tend to be as large. For example, we have found (14) significant correlations between axis V and job instability ($r=0.31$), housework neglect ($r=0.14$), and number of instrumental supporters ($r=-0.31$) but also many much smaller, insignificant correlations such as with marital instability ($r=0.06$), marital dissatisfaction ($r=0.09$), and job dissatisfaction ($r=0.07$). With diagnostic and demographic differences controlled, more symptom measures continued to exert an independent, significant effect on axis V ratings than did our social and occupational variables.

Axis V in *DSM-III* was conceptualized as a composite rating of adaptive functioning in three areas: social relations, occupational functioning, and use of leisure time. The only reference to symptoms was in the instructions for its use, where the manual states, "The highest levels of adaptive functioning should be used only when high occupational productivity is not associated with a high level of subjective discomfort" (p. 29). Several of the examples of scale points mention "distress" or "strain." In contrast, axis V in *DSM-III-R* "permits the clinician to indicate his or her overall judgment of a person's psychological, social, and occupational functioning . . ." (p. 20) and includes specific symptoms for each of the nine levels of functioning described.

The new Global Assessment of Functioning Scale of *DSM-III-R* axis V differs from the GAS in a number of respects. First, it is a 90-point scale rather than a 100-point scale; the highest interval (91–100 in the GAS), for unusually superior functioning, was deleted because it was anticipated that the scale would only be used in treatment settings where such high functioning would not be observed. Second, the rating on the Global Assessment of Functioning Scale is made for current functioning and highest level of functioning for a few months during the past year, whereas the GAS usually rates functioning for the week before an evaluation. The GAS gives explicit instructions to rate the lowest level of functioning in cases where levels of symptoms and social or occupational functioning might be in conflict and to disregard the need for treatment in making the rating; the Global Assessment of Functioning Scale gives no such instructions. Finally, the Global Assessment of Functioning Scale includes several behaviors specific to children, derived from the Children's Global Assessment Scale, in its illustrations; the GAS includes only adult behaviors, although it has been used to rate children.

Our findings have considerable significance for the revision of axis V in *DSM-III-R*. That clinicians include symptom levels in their ratings of adaptive functioning, even when they are not instructed to do so, may be taken as support for changing axis V toward the GAS. The revision merely standardizes the already prevailing clinical practice and brings axis V conceptually closer to what clinicians do, thereby promoting its usefulness. Symptoms such as delusions and hallucinations may exert their effects independent of the diagnosis, for example of schizophrenia, because they occur in other diagnostic groups as well or because of their variability within the group of patients with the diagnosis.

On the other hand, axis I diagnosis already bears a strong relationship to axis V ratings, and variations on symptoms are stronger determinants of axis V than social and occupational factors and tend to decrease the significant contributions of the latter. Therefore, the explicit endorsement of including symptoms in the rating may make axis V even more redundant with axis I diagnosis. If a major objective of a multiaxial approach is the quasi-independent assessment of different domains relevant to a comprehensive psychiatric diagnosis (14), then an approach exactly opposite from that taken in *DSM-III-R* should be instituted. The guidelines for assessing social and occupational functioning should be expanded and directions given to consider symptoms only if high functioning causes subjective discomfort. This would mean a return to the conceptual basis of axis V as it was in *DSM-III*, but with better instructions regarding the evaluation of the important facets of social and occupational functioning to guide clinical judgments.

The GAS has been useful in measuring change over time in patient groups and for comparing the severity of illness between groups of patients with different diagnoses. Presumably, the Global Assessment of Functioning Scale would have the same usefulness. Certainly, however, under the new *DSM-III-R* system, axis V will be less useful as an independent prognostic indicator of the outcome of an axis I disorder, since it may be so strongly related to diagnosis and symptom types. In addition, it may further obscure the relationships between symptoms, diagnosis, and impaired functioning. A further study should examine the effect of symptoms, as opposed to measures of social and occupational functioning, on actual *DSM-III-R* axis V

ratings in order to determine the best approach for *DSM-IV*.

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Foundation Funding and Psychiatric Research

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Support for psychiatric research is limited to a relatively small number of funding sources. Foundations—nonprofit entities that support a variety of social, medical, educational, and other activities—are a potentially important source. The authors describe the role and structure of foundations, discuss historical trends in foundation support for research in mental illness, and present the results of a study of the extent to which foundations support mental health research. The results of this study confirm the paucity of foundation support for mental health research but show important differences and similarities among the foundations that support research in this field.

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Notwithstanding exciting and substantial progress in both psychiatric research advances and public awareness and understanding of mental illnesses, federal support for biomedical and behavioral research into these disorders has been insufficient (1). Psychiatric research has been more uniformly dependent on federal funding than have other fields of biomedical and behavioral research (2). An increasingly diversified approach to financing research into mental illnesses must be adopted. The field must become cognizant of other avenues of research support, looking to individual state departments of mental health, to increased collaboration with industry, and to public and private philanthropies.

In this paper we will evaluate the current state of one such alternative funding mechanism—foundations. We will describe the role and structure of foundations, discuss historical trends in foundation support for research in mental illness, and present the results of a study that systematically reviewed foundation reports to determine the extent to which foundations support mental health research and the characteristics of the foundations that do so.

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THE ROLE AND STRUCTURE OF FOUNDATIONS

Foundations constitute an important but highly competitive source of nonfederal funding for research. Each functions as a "nongovernmental, nonprofit organization having a principal fund of its own, managed by its own trustees or directors and established to maintain or aid social, educational, charitable, religious, or other activities serving the common welfare" (3). Thus, foundations are institutions chartered for the express purpose of devoting private wealth to public causes. In 1985, philanthropic grants, gifts, and other contributions from foundations totaled $4.3 billion (4).

Foundations possess two distinct attributes that create flexibility, enabling them to initiate innovations and social changes in a manner quite distinct from either governmental granting agencies or private corporations. Unlike government entities, foundations possess uncommitted funds that can be used to support new projects relatively quickly. Unlike either corporations or government agencies, they are not bound by the fear of losing future support from Congress or shareholders for supporting controversial activities, since their funds are either endowed or expected to come from reliable donors. In comparison, government-operated programs and many corporations may be substantially more restrained. Foundations, therefore, have the resources and the independence to experiment with the unknown and the unconventional (5).

Both the scale and nature of foundation funding "offer a case where a technically private asset is of such potential value to the nation that it must, perforce, be regarded as a public asset" (6). Thus, "the public cannot afford to regard with indifference how foundation funds are spent, so precious are they . . . in the vital process of social change, and so limited are they in amount."

Public policy makers have not been indifferent to the conduct of foundation funding. They have acted as both competitors in financial largess and as regulators of foundation activities (7). Increasing regulation of private philanthropies, however, has had the effect of making greater amounts of information available to the public and to grant seekers.

According to *The Foundation Directory* (8), the Internal Revenue Service Organization Master File reveals that there are approximately 23,600 active fund-

ing foundations in the United States. Although each receives funds from one or more donors, much variability exists in the source of funds, the composition of the decision-making body, and the nature of the funded activities themselves. *The Foundation Directory,* which records information for about 4,402 of the most active foundations, has established four functional categories into which the majority of foundations may be grouped. These are 1) independent foundations, which are established for the purpose of aiding charitable activities, 2) company-sponsored foundations, which are independent grant-giving entities with close ties to a corporation that makes endowments, 3) operating foundations, which use their resources to conduct research or provide direct service, and 4) community foundations, which are publicly supported and make charitable contributions in a specific geographic region or community.

The management of a foundation involves the articulation of its philanthropic purpose or purposes and the formulation of the scope, requirements, and processes surrounding its funding activities. Because few restrictions are imposed by federal regulation, a foundation's donors and board of directors have wide-ranging flexibility to determine both the fields of interest and types and amounts of support to be proffered. However, many foundations prefer to concentrate specifically on certain subject areas, to both forward the goals of the foundation and to avoid "scatteration giving" (3). Having stated their interests, foundations generally will consider grant proposals that are related to their areas of interest. Some foundations, however, may be allowed to initiate special programs on an ad hoc basis, with either open or closed competition among potential grant recipients.

FOUNDATION SUPPORT FOR MENTAL HEALTH RESEARCH

Historically, few foundations have identified research on mental illness as a focus. In the early 1930s, Alan Gregg, then at the Rockefeller Foundation, sought to organize "the adequate endowment of five or six centers of psychiatric and neurological research" by 1946 (9). Although this plan never reached fruition, Gregg is credited with bringing psychiatry "from the outlying asylums [to become] scientifically respectable among the other academic depths of medicine [and] . . . psychiatrists did appear on the scene who were capable of carrying out their own basic research" (9).

In 1953, two decades after Gregg's attempt, Charles B.G. Murphy and Fritz Redlich established the Foundations' Fund for Research in Psychiatry. Murphy, a millionaire, provided the personal motivation and the funds for the foundation when Redlich, a psychiatrist heading the Department of Psychiatry at Yale University School of Medicine, informed him of the enormous need for research in psychiatry. In 1981, after 28 years, operation of the Foundations' Fund for Research in Psychiatry was terminated for lack of funds (10).

A number of smaller foundations (the Ittleson Foundation and the van Ameringen Foundation, for example) have focused on mental health issues but not specifically on psychiatric research. Several substantially larger foundations, such as the John D. and Catherine T. MacArthur Foundation and the Robert Wood Johnson Foundation, have initiated support for specified areas of mental health research based on the growing promise of the field.

Only in the mid-1980s has another single-purpose foundation emerged in the area of mental health research. Endowed through a variety of public and private sources in the wake of major breakthroughs in psychiatric research, the National Association for Research in Schizophrenia and Affective Disorders, established in late 1986, has just made its first two rounds of research awards.

In 1978 the President's Commission on Mental Health (11) reported that private sector support of mental health research—3.5% of the total of federal and private support to mental health research—was "shockingly low." The American Psychological Association (12, p. 308) reported that mental health grants—of which mental health research may be only a small subset—made up only 1.1% of the total grant dollars ($1.5 billion) in 1982. By 1984, the percentage rose by only 0.6% to 1.7% of the $1.6 billion in grants given.

The Institute of Medicine's 1984 report, *Research on Mental Illness and Addictive Disorders* (2), similarly reported that fewer than 30 of the nation's 970 largest foundations funding on a national or regional basis registered an interest in grants in the areas of mental health, psychiatry, or psychology. The Institute of Medicine concluded that given the rising tide of progress in the field of mental health research, support should be much higher.

The paucity of funding from the private sector—particularly from foundations—for mental health research prompts several questions that our study sought to answer through predominantly descriptive means. What is the extent of support from foundations for mental health research today? Can systematic distinctions be made between those philanthropies which support mental health research and those which do not? What are those differences? Last, what are the prospects for future support? To respond to these questions, we examined foundations for evidence of support for mental health research in much the same way a typical grant seeker would pursue the task.

METHOD

Data Sources

The Foundation Center of Washington, D.C., one of several regional foundation resources, is a repository

of descriptive and statistical data on the more than 23,000 U.S. foundations registered with the Internal Revenue Service. The following reference sources were used to compile the data.

1. *The Foundation Directory, 10th ed.* (8), coupled with the 1986 supplement (13), contains information on the 4,402 foundations that represented 97% of the total assets and 85% of the total grant dollars expended by U.S. foundations in 1983. Foundations listed in this directory either hold assets of at least $1 million or distribute more than $100,000 to outside organizations in the particular reporting year.

2. The *Foundation Grants Index Annual, 15th ed.* (14), provides annual information on grants in amounts of $5,000 or more made by more than 400 of the largest U.S. foundations.

3. The Foundation Grants Index computer database and Comsearch printouts provide on-line information comparable to that available through *The Foundation Directory* and the *Foundation Grants Index Annual.*

4. *Source Book Profiles* (15) contains in-depth information on the 1,000 largest foundations, detailing the purpose of the foundation, general types of support offered, financial data, grant analyses, and sample listings of grant recipients.

5. Internal Revenue Service Form 990-PF is a reporting form that all private foundations are required to file. These forms provide yet more information about grant-giving patterns of individual foundations.

6. *The American Psychological Association Guide to Research Support* (12) contains short profiles of foundations that have funded behavioral research.

7. Ten to fifteen percent of all philanthropic foundations also issue annual reports. These voluntary documents provide another corroborating source of information about grant-giving activities and funding patterns. They also often contain specific guidelines for grant development and submission of requests.

Data Collection

For the period 1983–1985, the most recent years for which information was available for all foundations, two separate data gathering mechanisms based on differing assumptions were used to generate the list of foundations evaluated in this study. The first approach was based on the assumption that the foundations most likely to support mental health research are those with a stated interest in the field of mental health in general. Thus, foundations with an identified interest in mental health, as recorded in *The Foundation Directory,* were identified. The following data were then collected on each: 1) the foundation's special area of interest, 2) support for research in general (stated, unstated, or excluded), 3) grants given for mental health research, 4) assets and range of grant size, and 5) geographic focus (whether giving is national, regional, or local in nature). If a foundation identified in this manner demonstrated grant support for mental health research, its future funding support in the field was assessed.

The second mechanism, complementary to the first, reviewed the Foundation Grants Index computer database to identify foundations that had given at least one grant for mental health research in 1983–1985. Although this included a number of the foundations located by using the first procedure, it also was able to identify foundations supporting mental health research whose charters do not make such support explicit. As noted previously the Foundation Grant Index database is restricted to foundations giving more than $5,000 per grant. Nonetheless, for foundations so identified, the same financial, funding pattern, and demographic information was gathered. Future funding patterns were also assessed.

Because this study was based on observational data, only descriptive statistics were computed to enable us to highlight the primary sources of foundation funding for mental health research and to facilitate comparison of such funding sources with other foundations not so identified.

Definition of Variables

Four particular study variables require further elaboration and definition.

1. *Research support.* The Foundation Center's reference sources, such as *The Foundation Directory* (8, 13) and *Source Book Profiles* (15), identify specific types of foundation support, such as endowments, fellowships, building funds, and capital funds. For the purposes of this study, foundation support categories were scrutinized for the specific inclusion or exclusion of the term "research" as a funding category. Foundations that did not state a specific interest in or prohibition against giving grants for research were noted accordingly.

2. *Mental health.* Neither standard foundation reference sources nor individual foundations provide specific definitions of mental health. It is a term used by foundations to identify their interest in a broad range of mental health areas that include but are not limited to research, service delivery, prevention, and education.

3. *Mental health research.* Mental health research encompasses a wide range of areas, including the biomedical sciences, behavioral research, and health services research. For the purposes of this study, research on specific mental illnesses or mental illnesses in general, psychiatric research, and behavioral or biomedical research related to mental illness were considered. In the assessment of specific grant activities, research grants with the following components were considered mental health research grants: affective, emotional, and social development; psychopharmacology; neuropsychiatry; neuropsychology; psychosocial development; geriatric mental disorders; mental disorders of childhood and adolescence; and psychotic disorders. When type of research was specified, the grant descriptions tended to focus on clinical research rather than

on basic or health services research. Frequently, foundations provided only the amount of the grant and the organization receiving the grant. In such cases, we assumed that a grant to a research institution or a university department of psychiatry was directed to research and that a grant to a service-oriented organization was unrelated to research.

4. Future support for mental health research. To determine a foundation's future support for mental health research, a number of factors were considered. Based on the reference sources cited, we identified each foundation's interest in mental health, recent grants in the area, and specific programs for mental health research. Telephone confirmations were sought from those foundations with a history of giving grants for mental health research. Interviews were completed with staff of 22 of 44 identified foundations. Interviews could not be completed for the remaining 22 because interviewees could not be contacted, failed to respond to telephone communications, or failed to provide adequate responses during the telephone interview.

With the information gathered from both printed and oral sources, each foundation was then placed in one of three categories regarding future support for mental health research: highly likely, unlikely, or possible.

A foundation was placed in the highly likely category if it showed substantial commitment to mental health research (e.g., grants given for such research or a program in mental health that includes research). Telephone confirmations were obtained from seven of the eight foundations in this category.

Although some identified foundations may have given at least one grant for mental health research, committed funds for the coming years and telephone responses denying a direct interest in mental health research indicated that future funding would be unlikely. Three of the six foundations in the unlikely category responded to the telephone interview.

A foundation was considered a possible funding source under two circumstances: 1) it did not specifically prohibit giving grants for research in general or mental health research in particular or 2) there was no evidence of previous substantial commitment to mental health research in either stated foundation interests or giving patterns. Twelve of the 30 foundations in the possible category responded to the telephone interview.

RESULTS

We found a total of 63 foundations with an identified interest in the general field of mental health; 33 (52%) of these also indicated support for research in general. Surprisingly, only 15 of the 63 foundations so identified actually had made grants for mental health research.

We also identified 29 foundations that, although they did not list mental health as an interest, had given grants for mental health research. Thus, of the 4,402 foundations reviewed for the study period, 44 (1%) made grants in the field of mental health research, even though 29 (66%) had no stated interest in the field.

TABLE 1. Interest in Mental Health Research and Other Characteristics of Major U.S. Foundations

Characteristic	Foundations That Awarded Grants for Mental Health Research (N=44)		Foundations With Interest in Mental Health Research (N=63)[a]		All Major Foundations (N=4,402)	
	N	%	N	%	N	%
Geographic focus						
National	19	43	18	29	1,434	33
Local	25	57	45	71	2,968	67
Type						
Independent	41	93	55	87	3,466	79
Company-sponsored	1	2	2	3	725	16
Operating	0	0	0	0	79	2
Community	2	5	6	10	134	3
Assets (in million dollars)[b]						
≥100 million	10	23	4	6	96	2
50–99	7	16	4	6	94	2
25–49	6	14	6	10	177	4
10–24	15	35	9	15	458	10
5–9	2	5	11	18	590	13
1–4	3	7	23	37	2,318	53
< 1	0	0	5	8	682	15

[a]Includes 15 of the foundations that awarded grants.
[b]Data on assets for one foundation were not available. Percents of foundations that awarded grants for and foundations with an interest in mental health are based on N=43 and N=62, respectively.

Table 1 shows the geographic focus, type, and assets of the 44 foundations that had given at least one grant for mental health research and the 63 foundations with an articulated interest in mental health compared with the 4,402 foundations listed in *The Foundation Directory* (8).

Generally, the foundations with an articulated interest in mental health appeared to be more similar to the larger group of 4,402 foundations than they were to the 44 foundations that actually made grants for mental health research, even though 15 of the foundations with an interest in mental health had made such grants (see table 1).

The foundations that actually made grants to mental health research were also evaluated on their likelihood to continue such giving in the future. Eight of these 44 foundations were judged to be highly likely to continue such support in the future. Thirty foundations were judged to be possible future funding sources. The six foundations considered unlikely sources of future mental health research funding had indicated such restrictions as "no grants for research," "funds already committed," or "service delivery and care projects only." Table 2 shows the areas of interest of foundations that

TABLE 2. Likelihood of Future Grants in Mental Health and Other Areas by Foundations That Previously Awarded Grants for Mental Health Research

Area of Interest	Likelihood of Future Grants: Highly Likely (N=8)	Possible (N=30)	Unlikely (N=6)	Total (N=44)
Mental health	6	9	0	15
Medical research	0	4	0	4
Other defined areas	2	5	1	8
Broad interests	0	12	5	17

awarded grants for mental health research according to their likelihood of making future grants.

Overall, foundations gave grants for at least four particular reasons. First, they had a specific program in mental health (e.g., the MacArthur Foundation, Grant Foundation, van Ameringen Foundation, Will C. Hogg Foundation, Ittleson Foundation, Della Martin Foundation, and John Harper Seeley Foundation). Second, they gave a grant for mental health research because of its relevance to their major area of stated interest (e.g., the Buhl Foundation, Retirement Research Foundation, Spencer Foundation, and Foundation for Child Development). Third, they supported medical research generally (e.g., the Burroughs-Wellcome Foundation, Pfeiffer Foundation, Charles Hood Foundation, and W.M. Keck Foundation). Fourth, they had broad interests and are open to different projects (e.g., the Meadows Foundation, Starr Foundation, W.S. Farish Foundation, McGraw Foundation, and Towsley Foundation).

DISCUSSION

By examining both the stated interests and funding patterns of foundations, we found that only 15 of 63 foundations which stated an interest in the field of mental health made grants in support of mental health research per se. The demographic and fiscal characteristics of these 63 foundations are similar to those of the 4,402 foundations in *The Foundation Directory*. That is, about 70% maintained a locality-oriented giving pattern and more than 50% held assets of less than $10 million.

In contrast, among the 44 foundations identified as having actually made grants to mental health research, more than 50% held assets of $50 million or more and almost half were nationally oriented. Given the high-cost, high-technology nature of biomedical and behavioral research projects, it is not surprising that support has been from predominantly larger, wealthier foundations.

Only eight of the 44 foundations supporting mental health research were judged to be highly likely sources of future funding; six were clearly unlikely funding sources. The remaining 30 possible sources of mental health research support should be the focus of further investigation.

These results attest first to the paucity of foundation funding sources for mental health research. Admittedly, the study's bias toward larger foundations (because of the high cost of mental health research and the selected $5,000 threshold in grant size) may have led to the exclusion of a number of foundations. Yet, discovering only eight highly likely sources of future funding was a surprise and a disappointment. However, the finding that a number of foundations with no directly stated interest in mental health actually made grants in mental health research gives rise to cautious optimism.

Since mental health problems are prevalent, affecting many groups of people, and since mental health research requires multidisciplinary investigation, any foundation concerned with research-related components can be approached. As the public becomes increasingly aware that mental illnesses are diagnosable and, in many cases, treatable, and as the excitement and vigor of the psychiatric research enterprise are transmitted to the public, foundations may discover a new interest in supporting mental health research. One means of heightening the awareness of foundations is through individual contacts with foundation officials and staff and the submission of high-quality grant proposals.

CONCLUSIONS

This examination of foundation funding patterns for mental health research suggests a number of other research activities in the area of foundations and other nonfederal sources of support for psychiatric research. Variables not considered in this study that might affect funding patterns—the interests and background of foundation boards of directors, foundation donors, and even foundation staff, for example—should be investigated. Further research should consider other ways of assessing foundation funding for biomedical and behavioral research, including surveys of potential research scientist grant recipients themselves. Parallel research examining corporate support for mental illness research would also be useful.

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A Curriculum for Education in Geriatric Psychiatry

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The authors present recommendations for educating medical students and psychiatric residents in geropsychiatry. They are primarily concerned with the objectives and methods rather than the content of training. Proposals are structured in terms of training objectives and educational settings in which such training takes place. The proposals are intended to be specific enough to be truly useful and at the same time sufficiently generalizable to adapt to geropsychiatric training in a variety of institutions. Priority is given to integrating knowledge of normal and abnormal aging with the clinical skills and empathy necessary to approach patients with competence and understanding.

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There is a growing need for effective and systematic education in geriatric psychiatry (1–5). In the past 15 years, our society has strengthened its commitment to geriatric care. The medical profession, in particular, has extended support for the elderly in programs for delivery of services and for training and research. These developments have found expression within the province of geriatric psychiatry, where education and research programs have received support through evolving commitments at the community, state, and federal levels (4). In this report we will present a set of recommendations for curriculum development in geriatric psychiatry. These recommendations grew out of a 1982 National Institute of Mental Health (NIMH) grant given to APA to develop a model curriculum in geriatric psychiatry for medical students and psychiatric residents.

Previous publications have emphasized curriculum content in mental health and aging, describing curricula for both resident (3, 4, 6) and fellowship (1, 2, 5, 7, 8) programs. These curricula have a broader applicability, both to medical students and to nonphysician trainees (2, 7). They address normative and pathological aspects of aging and describe the assessment and treatment of psychiatric disorders in the elderly. They place a premium on understanding the older person's social and physical environment. To surmount attitudinal obstacles to working in the field of aging, curricula universally highlight educational procedures for helping trainees overcome negative biases toward the elderly, a goal that has direct benefits for patient care as well.

These content areas are contained in the curriculum content outline included in this paper. A related bibliography is available on request. However, the emphasis of this report is on the structure rather than the content of a training curriculum. Lazarus and Weinberg (4) were also concerned with the process of program development in geriatric psychiatry. In addition to describing the diverse clinical and didactic experiences that make up trainees' involvement with normal and impaired elderly persons, they emphasized administrative issues such as developing alliances with institutional administrators, departmental chairpersons, and directors of residency training. They also urged that faculty be "chosen not only because they possess substantive knowledge in the field but also because of their ability to inspire and to teach." Eisdorfer and Cohen (2) presented overall training objectives for a 2-year program in mental health and aging. They underscored the importance of skills in administration, leadership, interdisciplinary collaboration, and research. A report by the Group for the Advancement of Psychiatry (GAP) (9) discussed several approaches to the format and setting of residency training in geropsychiatry. It also provided descriptions of several specific programs and offered suggestions regarding the general approach, content, and resource materials for such training.

Our curriculum recommendations differ from those of others in that we have not described the organization of a particular training program at a particular institution. Rather, we have developed recommendations that are intended as guidelines for programs at many institutions. In doing so, we attempted to integrate two competing aims. On the one hand, we

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sought to provide a structured and graduated set of experiences that will be specific enough to be truly useful in program design. On the other, we tried to incorporate a degree of generality which would ensure that the curriculum could be adapted to a variety of clinical and educational environments. This was not an easy task, nor one likely to meet with unanimity. We hope that programs wishing to develop or modify their training in geriatric psychiatry will find that we have reached a useful balance between these goals.

With these goals in mind, we propose a wide range of training experiences. We do not expect that many educational programs will be able to realize all of them. Therefore, to help others adapt the proposals to their own resources, we distinguish between those experiences which are essential and those which are supplemental or recommended. Thus, essential objectives should be attainable in virtually all general psychiatry training programs, but recommended experiences require additional resources or special interests on the part of residents or training programs. It is this distinction which should make it possible for many programs to match their educational resources—both programs and personnel—to the proposed curriculum.

OUTLINE OF PROPOSED CONTENT CURRICULUM

The content curriculum is intended to assist in the overall design of teaching programs. As such it is not elaborated in the detail actually needed by those who must make formal presentations on any of these topics. Organizationally, the content curriculum is presented in terms of the biopsychosocial framework, whose utility in geriatrics is widely appreciated. Methodologically, many approaches are feasible, ranging from lectures and seminars to case conferences, case-centered supervision, and community visits to homes, community centers, and institutional residences, where the lives of the elderly may be appreciated more directly. Commercial and educational sources offer valuable films, videotapes, and educational cassettes on numerous topics (10–12). These may be used to supplement videotapes selected from one's own institution or clinical practice. In all instances, it is recommended that the clinical and formal teaching activities be complemented by reading lists and topic outlines.

I. Normal Aging
  A. Conceptual problems
    1. Defining normal versus abnormal aging
    2. Distinguishing aging from cohort effects
    3. Advantages and disadvantages of cross-sectional and longitudinal studies
  B. Socioenvironmental
    1. Demography
      a. Changing composition of society
      b. Heterogeneity of the elderly (young old versus old old)
      c. Social, economic, and environmental consequences of demographic changes
    2. Attitudes and beliefs about normal aging
      a. Self-perceptions of the elderly and perceptions of physicians and the lay public regarding aging
      b. Myths about aging
      c. Attitudes toward death, illness, and dependency
      d. Cross-cultural and historical perspectives
    3. Social stressors in late life
      a. Retirement
      b. Widowhood
      c. Victimization
      d. Role change
        i. Role reversals of aging parents and their children
        ii. Caregiver, care receiver, homemaker, employee
    4. Support systems for the elderly
      a. Family
      b. Community
    5. Legal and ethical issues
      a. Competence and guardianship
      b. Treatment goals for the dying and demented
      c. Durable power of attorney
      d. Informed consent
      e. Role of the family in decision making
    6. Economics of late life
      a. Income: sources, poverty
      b. Expenses: housing, food, medication, transportation
      c. Medical care
        i. Costs of care: routine and long-term care
        ii. Sources of payment
        iii. Access to long-term care: the limitations of Medicare and Medicaid
  C. Psychological and psychosocial
    1. Developmental perspectives
      a. Theories of aging processes (e.g., disengagement and activity theory)
      b. New roles: grandparent, widow, retiree, caregiver, care recipient
    2. Cognitive perspective
      a. Age changes in memory, problem solving, speed, intelligence
      b. Capacities spared versus impaired
    3. Affective perspectives
      a. Normal moods in late life
      b. Grief
    4. Normal responses to physical decline, illness, and incapacity
  D. Biological
    1. Theories of aging
    2. Implications of altered homeostatic capacities
    3. Age-related changes in organ systems
      a. Cardiovascular

b. Neurological
c. Special senses
i. Auditory
ii. Visual
d. Renal
e. Genitourinary
f. Gastrointestinal
g. Respiratory
h. Endocrine
i. Dermatological
j. Musculoskeletal
4. Pharmacotherapeutic implications of biological changes
a. Pharmacokinetics and pharmacodynamics
b. Psychopharmaceuticals
i. Antidepressants
ii. Lithium
iii. Minor tranquilizers
iv. Major tranquilizers
c. Other drug classes (inclusion based on frequency of side effects or drug-drug interaction)
i. Cardiotonics
ii. Antihypertensives
iii. Antiepileptic drugs
iv. Antiparkinsonian drugs
v. Others (e.g., cimetidine)
d. Drug interactions
e. Prescribing principles
5. Sexuality in late life
a. Normative data: attitudes, activity, biological changes
b. Sexual dysfunction
i. Prevalence
ii. Etiology
iii. Interventions
6. Nutrition and exercise

II. Psychopathology of Late Life

A. Approach

Topics in this section are organized by syndrome and, in some instances, by etiology (e.g., substance abuse). The order in which topics are listed roughly indicates their recommended priority. Priority judgments reflect the prevalence of the disorders in clinical populations or a judgment as to the critical role physicians have in their evaluation (e.g., psychiatric presentations of medical illness). Within each category of psychopathology, it is recommended that the traditional, medically oriented approach be used in organizing information, with the understanding that this implies use of a biopsychosocial approach. Thus, the following outline would guide the selection of material for discussion of each topic.

1. Epidemiology
2. Clinical presentation
3. Pathogenesis
4. Diagnosis
a. Criteria
b. Laboratory procedure
5. Differential diagnosis
6. Treatment
a. Psychosocial
b. Somatic

B. Topics

1. Affective disorders
2. Dementia
3. Late-onset psychoses
4. Delirium
5. Psychiatric presentations of medical illness and medical manifestations of psychiatric disorders
6. Iatrogenesis
7. Anxiety disorders
8. Disorders of sleep
9. Substance abuse
10. Influence of aging on disorders of earlier onset (e.g., schizophrenia and mental retardation)

OUTLINE OF TRAINING CURRICULUM FOR MEDICAL STUDENTS

The training curriculum recommendations for medical students provide guidelines for integrating appropriate material from the content curriculum with students' clinical training in psychiatry. The overall objective is to provide clinical exposure based on knowledge of normal development and psychopathology of late life. The major headings in the following sections identify topical areas rather than year of training (in parentheses), since individual medical schools vary in the year in which, for example, a course in normal development is offered. Nevertheless, we have adhered to a logical and, we hope, a compatible sequence of training proposals. Throughout, collaborative arrangements with other specialty areas are encouraged to ensure a multidisciplinary approach to each topic.

I. Normal Aging (year 1)

A. Objective: fundamentals of normal aging

B. Setting: course in human development

1. Exposure to patients through live or videotaped interviews
2. Didactic or seminar presentations of core factual information (presented in section I of the outline of proposed curriculum content, A–D)

C. Experience

Through a combination of formal presentation and patient exposure, medical students should become familiar with the distinctive characteristics of normal aging. A balanced presentation of its challenges, opportunities, stresses, and losses should be sought. Emphasis should be given to such age-related difficulties as sensory

impairment, functional incapacity, and adaptation to retirement, disease, dependency, and death. These experiences should provide the factual and experiential foundation that will permit elderly patients to be approached with knowledge and a genuine sense of understanding.

II. Introduction to Late-Life Psychopathology and Clinical Assessment (year 2)
  A. Objectives
    1. Fundamentals of geriatric psychopathology
    2. Introduction to clinical assessment of elderly patients
  B. Settings
    1. General psychiatry-psychopathology course (or alternate course setting in which this material is presented)
    2. Course in clinical interviewing or diagnosis
  C. Experience
    Through participation in lectures, clinical demonstrations, and assessment exercises, students should acquire knowledge of the fundamentals of late-life psychopathology. Section II of the content curriculum outlines the approach and content of such presentations and indicates that priority should be given to those syndromes and disorders which are characteristically of late onset (e.g., dementia) or whose presentation is distinctive in late life (e.g., affective disorders, paranoid disorders, and medical illness). Students' introduction to clinical diagnosis and interviewing should include participation in the assessment of elderly patients with diagnoses in at least two of these areas.

III. Clinical Clerkship in Psychiatry (year 3)
  A. Objective: application of knowledge acquired in years 1 and 2 to the clinical care and management of elderly patients
    1. Participation in the diagnostic evaluation and treatment of at least one elderly patient with depression and one with dementia
    2. Attainment of basic competence in performing and interpreting a clinically oriented mental status examination with emphasis on cognitive function
  B. Settings: outpatient or inpatient components of psychiatry clerkship
  C. Experience
    During the psychiatry clerkship, the medical student is encouraged to integrate knowledge of normal aging and late-life psychopathology with the evaluation and treatment of elderly patients. The distinctive clinical problems and presentations of late-onset mental disorders may be underscored through direct case responsibility, coordinated clerkship lectures or seminars, and attendance or presentation at case conferences. Faculty with particular interest and knowledge in geriatric psychiatry should participate when possible.

IV. Electives in Geriatric Psychiatry (year 4)
  A. Objective: opportunity for clinical or research electives in geriatric psychiatry
  B. Settings: inpatient or outpatient services, a psychiatric consultation service in a general hospital, or exposure to long-term care programs and home care services
  C. Experience
    To take advantage of flexibility in the fourth year, structured and closely supervised electives in such settings as those noted may be developed. In addition, faculty with expertise in geriatric psychiatry may be encouraged to offer individualized programs of study, research, or clinical activity.

OUTLINE OF PROPOSED TRAINING CURRICULUM FOR RESIDENTS

I. General Objectives
  The psychiatric residency provides a variety of clinical and academic settings in which to acquire knowledge of and clinical competence in the care of the elderly psychiatric patient. Opportunities may be repeated throughout the training period, permitting skills and knowledge to be accrued and elaborated progressively. Thus, the following objectives are applicable throughout the residency.
  A. Working knowledge of multidisciplinary assessment and management, including competence in providing leadership to a geriatric multidisciplinary treatment team
  B. Competence in assessment of the older patient
    1. Interviewing skills
      a. Evaluation of distinctive losses and treatment resistances
      b. Recognition and pursuit of psychological and social issues germane to the older patient
    2. Competence in conducting the mental status examination
      a. Assessment of higher cortical functions with tact and respect for the patient's dignity
      b. Indications for and interpretation of neuropsychological testing
    3. Competence in community and environmental assessment
      a. Community and social services
      b. Legal issues
      c. Health care sponsorship
      d. Residential environments
    4. Competence in family assessment
      a. Personal, social, and financial resources
      b. Role of the family as caregiver
      c. Family burden

d. Indications for therapeutic interventions with the family
5. Competence in medical assessment of the older patient
a. General physical examination
b. Complete neurological examination
c. Selection of laboratory tests appropriate to medical and psychiatric findings

C. Formulation of psychological, social, and biomedical information into a multidisciplinary treatment plan

D. Competence in treatment of the older patient
1. Psychotherapy with the ambulatory elderly patient, including familiarity with grief and reminiscence therapies
2. Pharmacotherapy and other biomedical therapies, such as ECT, with emphasis on features that distinguish their application to the elderly
3. Coordination of community, environmental, financial, and legal interventions—including interventions for individuals unable to care for their own needs or resources
4. Treatments addressing the marriage or family of the older patient
5. Comprehensive management of dementias, delirium, and affective disorders, incorporating psychotherapy; pharmacotherapy; community, environmental, financial, and legal interventions; and marriage or family therapy

E. Ability to recognize and deal constructively with biased attitudes toward the elderly, both in oneself and in co-workers

II. Specific Objectives

A. Medical general hospital experience (PGY-1)
This experience contributes directly to the psychiatrist's responsibility for the management of patients' medical problems. The general medical experience contributes to knowledge of psychopharmacotherapy and an appreciation of the psychiatric manifestations of nonpsychotropic drugs and medical illness. In addition, this experience helps to build the resident's understanding of the impact of medical problems and health delivery systems on the lives of the elderly.
1. Objective: competence in the diagnostic evaluation and basic management of common medical illnesses of the elderly
2. Essential experience
a. Clinical experience entailing primary physician responsibility for medically and, if feasible, surgically ill elderly patients, including a teaching program that involves attending rounds, case conferences, and other educational environments
b. The spectrum of problems seen should include patients with cardiovascular, renal, and hepatic illness as well as other medical problems seen frequently in the elderly, such as injuries from falls, incontinence, iatrogenic disorders, and confusion
3. Recommended: clinical rotation on a geriatric evaluation unit

B. Inpatient geriatric psychiatry (PGY-2)
1. Objective: acquisition of skills and knowledge needed for diagnosis and treatment of major mental illnesses in the elderly
2. Essential experience
a. Responsibility for the care of patients with dementia and depression
The patients should provide a spectrum of problems with respect to etiology, severity, and symptoms. The number of patients cared for should be sufficient to ensure knowledge and competence in these two major areas of late-life psychopathology. We recommend that residents have primary responsibility for at least three patients with depression and at least three patients with dementia
b. Didactic experiences
i. Normal developmental issues, as viewed within a biopsychosocial framework
ii. Psychopathology: nosology, phenomenology, and differential diagnosis of late-life mental disorders, with emphasis on disorders that are characteristically of late onset (e.g., dementia), disorders whose presentation may be altered in late life (e.g., affective disorders), and psychiatric manifestations of physical illness
iii. Interviewing skills and principles of psychotherapy
iv. Clinical psychopharmacology and ECT for the elderly
v. Demography and social stressors in late life
vi. Use of the health care system
3. Recommended: full-time, 3-month clinical rotation on a geropsychiatry unit or other inpatient service that includes a large fraction of elderly patients

C. Outpatient geriatric psychiatry (PGY-3)
1. Objectives
a. Strengthening of diagnostic and treatment skills through exposure to elderly outpatients
b. Development of competence in the management of grief and other losses of late life
c. Enhancement of appreciation of the spectrum of problems and competencies of elderly patients and their families
2. Essential experience

a. Clinical responsibility for patients
Age-related problems requiring the resident to use a variety of therapeutic modalities, including individual psychotherapy (both brief and long-term), family therapy, and pharmacotherapy, should be presented. The number of patients cared for should be sufficient to achieve this objective. We recommend five such cases.
b. Didactic and/or supervisory instruction
This instruction should address the knowledge base of these interventions, as outlined in the proposed content curriculum and the general objectives of residency training. The didactic program should be integrated with the didactic program included in the inpatient experience.

3. Recommended: continuous care responsibility for elderly patients
Such responsibility may be obtained in different ways, including co-leading a group for elderly patients; serving as primary therapist for an elderly patient, couple, or family involved in a long-term treatment process; and participation in a long-term care treatment facility or home care treatment service.

D. Psychiatric consultation for the elderly (PGY-3)
1. Objectives
a. Competence in providing diagnostic and treatment consultation for the hospitalized or otherwise institutionalized elderly patient
b. Competence in the recognition and treatment of delirium as well as other organic brain syndromes
c. Competence in collaborating with care providers in other medical and nonmedical disciplines
2. Essential experience
a. Clinical: as a member of such a service, the resident has the opportunity to assume responsibility for all aspects of psychiatric consultation to hospitalized elderly patients
b. Didactic: in the context of clinical supervision and formal teaching events, the institutional environment provides the opportunity to examine the interaction of sociocultural and political and/or economic factors in the lives of the institutionalized elderly patients
3. Recommended: community consultation
As part of the rotation in consultation-liaison psychiatry or another rotation offering the opportunity, the resident is encouraged to provide similar consultation for elderly patients who live in their own homes, in nursing homes, or in other long-term care facilities. Such experiences provide added opportunity for acquiring skill in the recognition and treatment of behavioral management problems and for promoting the development of realistic and positive attitudes of care providers toward elderly patients

E. Psychiatric emergency room-crisis intervention rotation (PGY-3)
1. Objectives
a. Competence in making rapid initial assessments and interventions in the management of elderly patients and their families presenting to the emergency room or crisis intervention center
b. Competence in initial diagnostic assessments, including carrying out appropriate physical, neurological, and laboratory examination and in arranging additional medical consultation as indicated
c. Competence in incorporating knowledge of family and community resources into the initial diagnostic and treatment plan
2. Essential experience: an emergency room-crisis intervention rotation providing service in a setting that receives referrals of elderly patients for evaluation

F. Elective opportunities (PGY-4)
1. Objectives
a. To provide the interested resident an opportunity to increase knowledge and clinical skills in geriatric psychiatry
b. To facilitate development of special interests in both the clinical and research aspects of geriatric psychiatry
2. Recommended: as permitted by the resources of a particular institution, the elective interests of residents may be supported by
a. Further clinical opportunities in any of the inpatient, outpatient, or community settings already mentioned
b. Identification of faculty who are carrying out research programs in which interested residents may participate or through whom residents may develop original, feasible protocols
c. Establishment of chief residency or fellowship opportunities in geriatric psychiatry
d. Organization of lectures or seminars in gerontology and geriatrics

EVALUATION

The improvement of any training program requires an effective evaluation process. Since the practices of individual institutions undoubtedly strongly influence

the approaches chosen, we confine ourselves here to general comments and suggestions regarding evaluation.

In a multidisciplinary field whose knowledge base is rapidly expanding, considerable effort is required by educators to make sure that the content of a curriculum remains balanced and current (13, 14). Mechanisms should be provided for evaluation of both trainees and the educational program and should distinguish individual competencies from the content and organization of the training program. A number of methods for evaluating attitudes toward the elderly and the fields of aging are available for consideration (2). In evaluating trainees' knowledge, we must depend primarily on evaluation of trainees' performance in clinical and supervisory activity, although factual tests would be desirable if they were available. Adapting the oral examination format for the training and evaluation process can be a valuable supplement to the traditional means for trainees and supervisors to work together. It should be noted that the Psychiatric Knowledge and Skills Assessment Program of APA includes a section on geriatric psychiatry. The Psychiatry Residency In-Training Examination (PRITE) also includes questions on geriatric psychiatry, although, as yet, there is no section devoted to it. A brief self-assessment examination intended for students and professionals has been published (15–17), but its utility as a means of evaluating either an individual's knowledge or a program's efficacy has not been validated.

CONCLUSIONS

Curriculum development is a dynamic process. The curriculum we have proposed will require change as the skills and knowledge needed for competence in geriatric psychiatry expand. The movement to have the American Board of Psychiatry and Neurology recognize added qualifications in geriatric psychiatry bespeaks not only the social value of caring for the elderly but the fact that it is possible now to define the field in terms of a substantial body of information and clinical skills. Directors of psychiatric training programs recognize that they must ensure opportunities for medical students and residents to become competent in this field.

We hope this proposal will serve as a heuristic device in geropsychiatric education. Our primary goal has been to describe the objectives and methods of such training for medical students and psychiatric residents. Other resources (reference 18, for example) provide in-depth information regarding a content curriculum for this area.

In developing this curriculum we have been cognizant of the fact that programs will vary in the aims and resources of their educational activities. Some will have smaller or primarily general psychiatric facilities, while others will be larger or more specialized. Similarly, some will aim to ensure competence for the general psychiatrist, while others will provide tracks that lead to added qualifications. To address these differences we have distinguished throughout this proposal between those experiences which we view as essential and those which are recommended, recognizing, of course, that even within this division there is room for discretion and diversity in program development.

Since the educational programs of medical students and residents are already crowded with information from many clinical and scientific disciplines, educators will probably find it difficult at first to give the fields of aging the attention that they need. Psychiatric residencies, in particular, are already closely regulated regarding the inclusion of knowledge from many such disciplines. We and others have found, however, that the changes involved are feasible and valuable. With time, the changes should become easier to implement. For example, in time we may be able to distinguish accurately between experiences which are essential for all psychiatrists and those which are more appropriate for psychiatrists who wish to specialize in geropsychiatry. Identifying areas that permit flexibility or electives will also facilitate the integration of geropsychiatric training with other components of medical student and resident training. For example, general psychiatry inpatient settings and consultation-liaison work provide many avenues for introducing geriatric principles.

Opportunities for research in geropsychiatry will continue to enrich students' education and will also help furnish the clinical and basic science investigators of the future. Ultimately, of course, we will judge the quality of training by the quality of psychiatric care received by elderly patients. We hope that our collective efforts to improve the education of medical students and residents in geriatric psychiatry will ensure tangible and ongoing improvements in the care of the elderly.

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Graphic Representation of the Life Course of Illness in Patients With Affective Disorder

Robert M. Post, M.D., Peter P. Roy-Byrne, M.D., and Thomas W. Uhde, M.D.

The authors illustrate methods for the graphic depiction of the course of unipolar and bipolar affective illness. The utility and advantages of such an approach include 1) accurate assessment of episode patterns, 2) elucidation of relationships to environmental events, endocrine and seasonal factors, and psychosocial stressors, 3) better delineation of treatment response, 4) a greater understanding of the longitudinal and characteristic patterns of illness, and 5) the associated better patient management with psychotherapeutic and pharmacological interventions.

(Am J Psychiatry 1988; 145:844–848)

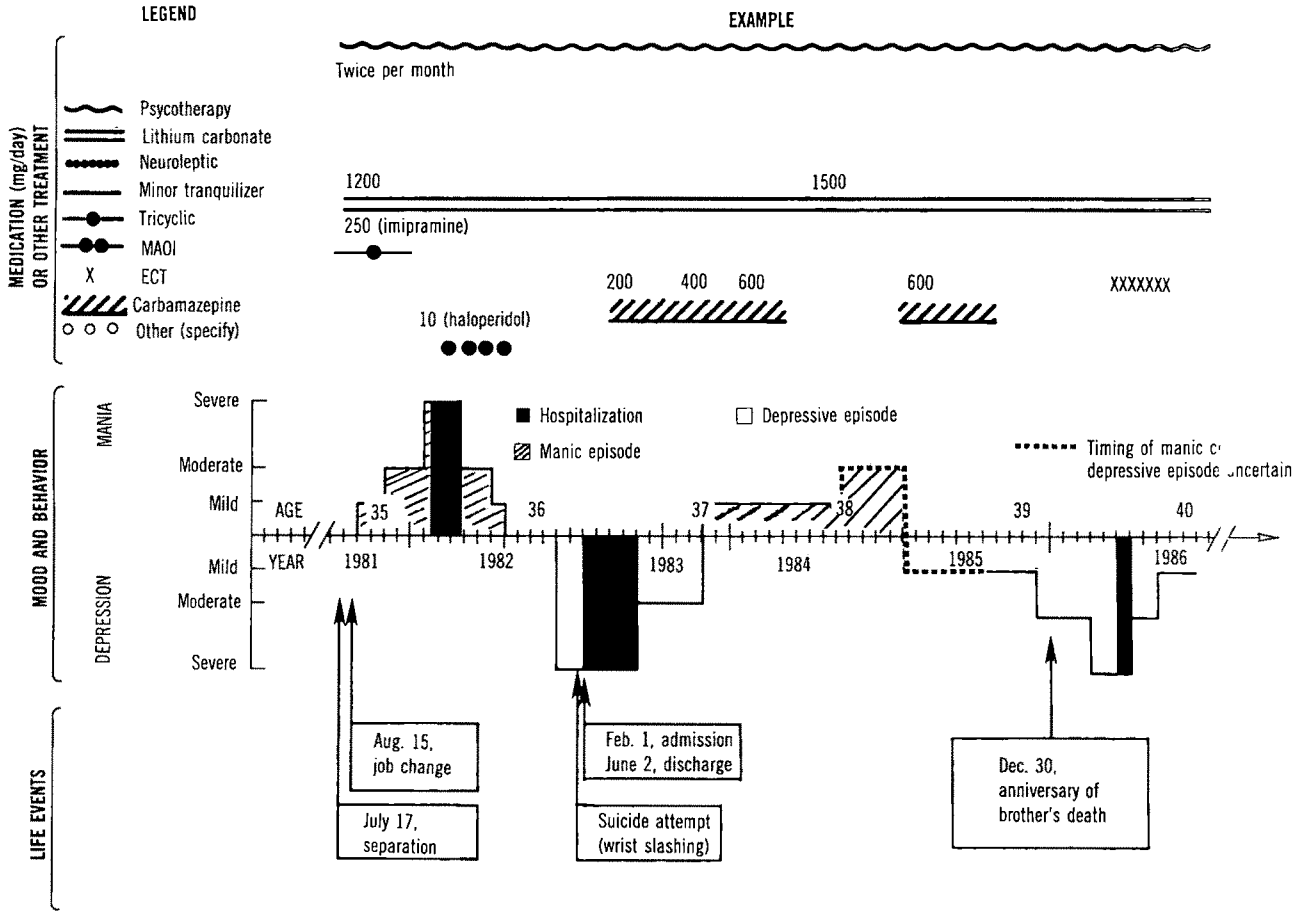
Kupfer and Rush (1, 2) have recommended the inclusion of additional clinical descriptions of affectively ill patients in clinical research reports. Among the recommended guidelines are an increased focus on the longitudinal course of illness and the duration of the current episode. We feel that these guidelines not only are appropriate for research designs but should be extended to routine clinical practice. Specifically, we recommend detailed graphic representation of the longitudinal course of affective illness.

This process appears indispensable to initial diagnostic assessment of the illness, formulation of appropriate recommendations for acute and chronic treatment, and, ultimately, accurate monitoring of the psychological and pharmacological interventions employed. Although there is increasing recognition of the recurrent nature of primary affective illness (3–6), parallel advances have not been made in systematic assessment and record keeping regarding affective episodes. Casual or even detailed written histories of major affective episodes, including psychiatric hospitalizations, do not adequately reveal the precise course, frequency, severity, or pattern of manic-depressive episodes in the majority of patients. Use of more systematic and precise measures would appear indicated. Similar life-charting methods have been used to evaluate the efficacy of lithium prophylaxis (7). They have also been used in the distant past by both Kraepelin (8) (to show the variability in course of illness in his patients) and Adolf Meyer (9) (to show the interaction between innate temperament, life stress, and disease).

Specifically, we recommend graphing the longitudinal life course of affective episodes according to three levels of severity that are easy to assess, even retrospectively, on the basis of degree of functional incapacity (10, 11). As illustrated in figure 1, severe depression or mania would indicate that the patient was essentially nonfunctional; solid shading of such an episode would indicate the patient was hospitalized. Moderate severity would reflect definite impairment in work or social function, while mild severity would indicate that the patient or relatives recognized mood or behavioral alterations distinctly different from their normal state but not causing impairment in social or occupational functioning. Only depressions meeting moderate or greater severity are counted as formal depressive episodes in order to provide a conservative estimate of number of episodes (10, 11). Charting of ongoing mild levels of depression with superimposed more severe episodes provides a basis for charting "double depression" (12) or interval symptoms (see references 10 and 11 for further details of the charting process). An appropriate code could also be adopted for charting important life events (below the mood line) and for different classes of psychopharmacological and psychotherapeutic interventions (above the line; see figures 1 and 2).

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FIGURE 1. Prototype for Charting the Life Course of Illness in Manic-Depressive Patients

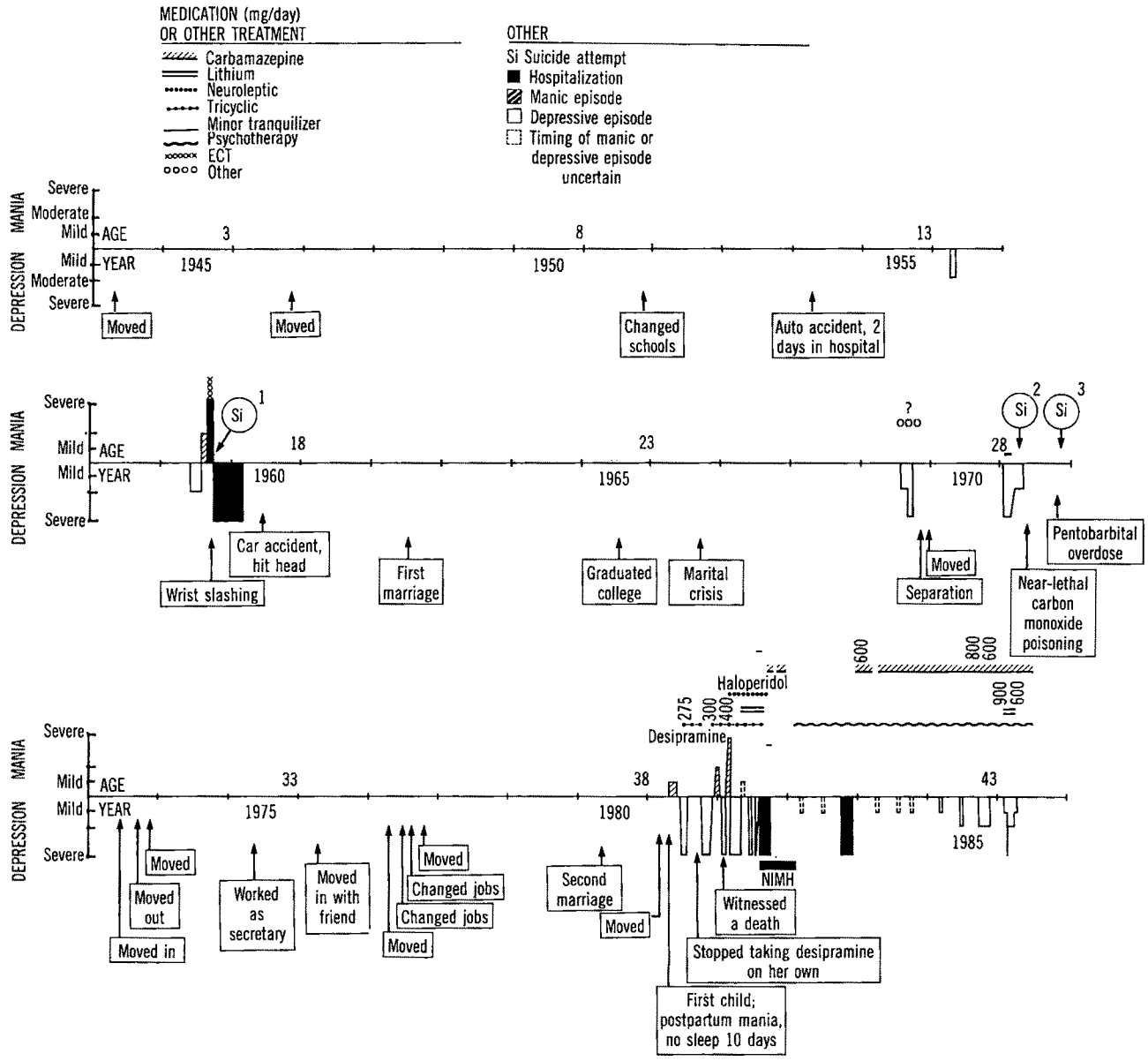


Data in this form can be gathered from the patient and related informants on the first interview and can be modified on subsequent visits as further detailed data are gathered from other sources, including previous physicians and hospital records, as well as calendars, diaries, and information from relatives and other sources. This also provides the opportunity for encouraging prospective plotting of the life course of illness, with the additional use of a visual analogue scale based on patients' assessments of their own mood daily on a 100-mm line on which 0=worst ever, 50=balanced, and 100=best ever. This process, which would take only several seconds to complete, could be linked to morning or evening medication ingestion or other behavioral routines of the day.

We encourage this retrospective and prospective plotting of the course of illness as an invaluable guide to the progress of therapy. In our experience, detailed graphic representation of the course of illness has revealed that previous medications such as lithium were, in some instances, misclassified as ineffective when they had clearly had a marked impact on the course of illness. It has also helped uncover instances where agents may have exacerbated the course of rapid cycling in the illness. As emphasized by Wehr and Goodwin (13) and their associates, tricyclic antidepressants and monoamine oxidase inhibitors in many instances may increase the frequency of cycling or precipitate rapid and continuous cycling of affective illness. Such relationships can be uncovered more easily once the longitudinal course of the illness is graphically represented in relationship to treatment. In our experience, removal of these agents, as recommended by Wehr and Goodwin (13) and their associates, has sometimes ameliorated the rapid cycling process. Accurate assessment of even partial response to a given prophylactic agent such as lithium becomes especially important in relationship to making recommendations for continuation of pharmacotherapy or use of combination therapy with other available agents, including carbamazepine and related anticonvulsants (14). Timing of periods of low risk (for possible medication-free evaluation) or periods of high risk (for possible institution of additional pharmacological prophylaxis) can be more appropriately addressed if a definitive pattern of recurrence has been uncovered in the graphing process.

Figure 2 illustrates the course of illness of a 43-year-old married woman with bipolar disorder who had a

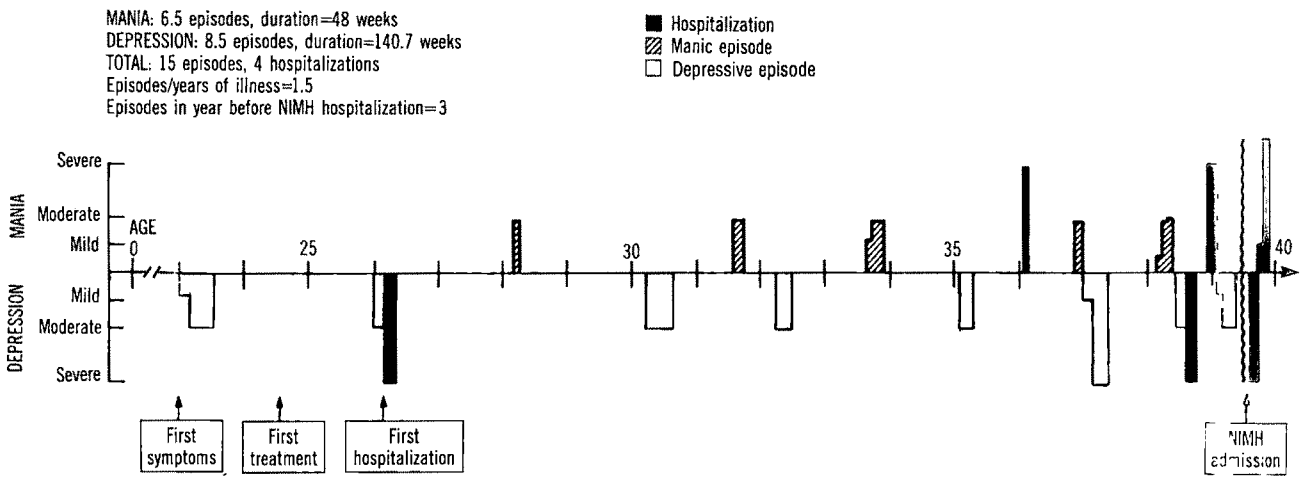
FIGURE 2. Life Chart of the Course of Illness of a Manic-Depressive Woman



history of depression at menarche and postpartum mania followed by rapid cycling potentially exacerbated by desmethylimipramine and not prevented by concurrent lithium and haloperidol, although these agents may have dampened manic episodes. Two auto accidents involved only mild head trauma. Three severe suicide attempts occurred near the onset or remission of depressions. The patient required hospitalization for mania at age 17 and for severe, incapacitating retarded depression at age 39 (at NIMH) and at age 40 (elsewhere). Both depressions responded to acute treatment with carbamazepine, but prophylaxis was only partially effective as depressive episodes of successively greater severity and duration began to emerge.

Figure 2 uncovers a wealth of data, intricate patterns, and temporal relationships and conveys this information in a concise graphic format. This patient is typical of many patients studied since the time of Kraepelin who tend to show an accelerating course of illness (4, 8, 10, 11, 15). The median course of affective episodes for 82 patients with bipolar disorder who were admitted to NIMH is illustrated in figure 3. This figure shows the progressive course of illness (shown by the decreasing length of intervals between episodes), despite the best available conventional treatment in the community. This pattern of illness also provides the basis for considering possible mechanisms accounting for the progression of episodes and possible novel interventions (15). Although these 82 patients represent a subgroup of severely ill and refractory patients in a tertiary referral center, less severely ill patients may also show a gradual, evolving course (4, 8) and

FIGURE 3. Median Course of Affective Illness in 82 Manic-Depressive Patients



benefit from close longitudinal monitoring of their symptom patterns and response to medications.

Another positive derivative of the graphing process is the potential earlier identification of premonitory symptoms that typically occur with manic and depressive episodes. Continuing the graphing process prospectively can be the basis for improved monitoring and titration of therapeutic regimens and detection of early signs of hypomania or depression characteristic of a particular individual. This early assessment and potential intervention may then help to abort more severe episodes.

Such a longitudinal assessment, perhaps equivalent to accurate monitoring of blood or urine glucose for the diabetic, can lead to better therapeutic management. In addition, compliance with psychopharmacological regimens may be enhanced on the basis of the collaborative nature of the process, the "medicalization" of the illness, recognition of previous patterns and high risk of recurrence and painful consequences, and "routinization" of record keeping and associated medication intake. The psychotherapeutic process may also be enhanced if the charting process helps to uncover previously unrecognized associations between the onset of episodes and anniversaries, life events, and seasonal and other patterns. Such a record kept by the patient and physician would also help in issues of continuity of care when a patient is transferred from one physician or hospital to another. Many of the benefits discussed would also be derived from systematic longitudinal assessment of other neuropsychiatric disorders, as demonstrated for panic disorder (16). As treatment options have diversified and become increasingly complex with the advent of multiple psychopharmacological modalities for intervening in both the depressed and manic phases of the illness (17), it would appear appropriate for assessment techniques to be enhanced in parallel, so that treatment strategies can be engaged most effectively.

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Effect of Psychosis on Suicide Risk in 1,593 Patients With Unipolar and Bipolar Affective Disorders

Donald W. Black, M.D., George Winokur, M.D., and Amelia Nasrallah, M.A.

The authors report suicide risk among 1,593 patients with major depression or bipolar disorder, 443 (27.8%) of whom were psychotic (260 bipolar and 183 unipolar). The subjects were followed for 0–14 years, and their suicide experience was compared with that of the state population. Eight (19.5%) of the 41 suicide victims were from the psychotic group. The psychotic and nonpsychotic subjects in each diagnostic group had similar risks for suicide. A higher risk for suicide was not found in the bipolar subjects. The authors conclude that among patients with major affective disorder psychosis per se does not predispose to suicide.

(Am J Psychiatry 1988; 145:849–852)

Most psychiatrists, clinicians, and researchers are aware that the most replicable risk factor for suicide is depression (1). What many may not appreciate is that, regardless of the clinical symptoms of depression (2), the specific subtype of depression (3, 4), and how the depression is treated (5), during a long-term follow-up a relatively high percentage of patients will commit suicide. In 1970, on the basis of available data, Guze and Robins (6) estimated that 15% of all persons with major affective illness will commit suicide. Further, the data suggest that severity, including the presence or absence of psychotic features at the time of ascertainment, probably has little to do with the natural history of depression and the likelihood that the cause of death during the follow-up will be suicide.

Despite these findings, the risk for suicide in delusional depression has been reported to be 5.3 times as high as in nondelusional depression (7). This finding was based on a retrospective study of patients who committed suicide in a New York hospital over a 25-year period. Of the 14 patients with unipolar endogenous depression who committed suicide, 10 were delusional. Psychosis was significantly more prevalent among the depressed suicide victims than among living depressed control subjects. The investigators concluded that delusions were among the most powerful predictors of suicide in patients with endogenous depression. They further hypothesized that the higher rate of suicide may be an intrinsic part of the delusional depressive syndrome. This hypothesis was based, in part, on research suggesting that delusional depression is a distinct clinical syndrome (8–10).

Because different subtypes of major affective disorder, including psychotic and nonpsychotic forms, appear to differ from both clinical and research perspectives, it is not unreasonable to postulate that each might have its own mortality risk. We decided to compare the suicide experience associated with well-defined subtypes of affective disorder. This was possible with a large data set, in which 2,054 patients with major affective disorder were identified, systematically rediagnosed, and followed up through a record-linkage process.

METHOD

Two thousand fifty-four patients with affective disorder were admitted to the University of Iowa Psychiatric Hospital between Jan. 1, 1970, and Dec. 31, 1981. Their charts were carefully screened by one of us (A.N.), and all patients were rediagnosed with the

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DSM-III criteria. We selected 1,593 Iowans for this study; 1,007 satisfied the *DSM-III* criteria for major depression and 586 for bipolar disorder. The patients were then further divided into those with psychosis and those without. Psychosis was considered present if the subject had delusions and/or hallucinations. We used the standard definitions for hallucinations and delusions presented in *DSM-III*. We have not used the term "psychotic features" since *DSM-III* includes stupor under this heading. If the patient had several hospitalizations during the study period, the most recent was considered the index admission.

Deaths were determined by electronically matching the 1,593 patients against Iowa death certificates for the period from Jan. 1, 1970, through Dec. 31, 1983. Multiple identifiers were used (e.g., name, sex, date of birth) to aid in the matching. Potential matches were then screened by one of us (A.N.) to determine true matches. Non-Iowans (7.4% of all patients with affective disorder admitted to our hospital) were excluded from the analysis because death certificates would not be readily available for them. Patients who moved from Iowa or changed their names after hospitalization were missed in follow-up, but because there was no personal follow-up we do not know how large this group is. During the follow-up, 157 (9.9%) patients died, 41 (26.1%) from suicide (*ICD-9* E 950 through 969).

To compare the observed number of deaths with the expected number, we adjusted for age, sex, and length of follow-up by computing mortality tables specific for these factors based on vital statistics and census data for Iowa. We did not adjust for race because so few Iowans are nonwhite (2.7%). The observed and expected numbers of deaths were tested by means of chi-square analysis with the Freeman-Tukey correction. A standardized mortality ratio was calculated for each comparison and represents the ratio of observed to expected deaths. A ratio greater than one means that the number of observed deaths exceeds expectation. Ninety-five percent confidence limits were then calculated for the standardized mortality ratios (11). Our methods have been reported elsewhere (12).

RESULTS

Of the 1,593 patients, 443 (27.8%) were psychotic. Within the diagnostic subgroups, 44.4% of the bipolar (N=260) and 18.2% of the unipolar (N=183) patients were psychotic, a significant difference ($\chi^2=138.68$, df=1, $p<0.001$).

We identified 41 suicides during follow-up, which ranged from 0 to 14 years. As table 1 shows, the percentages of deaths accounted for by suicides in the four diagnostic groups (psychotic and nonpsychotic major depression and bipolar disorder) were not significantly different. Overall, suicides accounted for 22.2% of the deaths among psychotic subjects and 27.2% of the deaths among nonpsychotic subjects. Eight patients (19.5%) who subsequently committed suicide were psychotic during their index admissions. One psychotic patient and one nonpsychotic patient committed suicide in the hospital; both had bipolar disorder.

TABLE 1. Deaths and Suicides Among 1,593 Psychotic or Nonpsychotic Patients With Major Depression or Bipolar Disorder

Disorder	N	Deaths		Suicides		
		N	%	N	% of Total	% of Deaths
Major depression						
Psychotic	183	20	10.9	6	3.3	30.0
Nonpsychotic	824	95	11.5	28	3.4	29.5
Bipolar disorder						
Psychotic	260	16	6.2	2	0.8	12.5
Nonpsychotic	326	26	8.0	5	1.5	19.2
Total						
Psychotic	443	36	8.1	8	1.8	22.2
Nonpsychotic	1,150	121	10.5	33	3.1	27.2

A comparison of the suicide experience of the study sample with that of the general population involves a comparison of the observed and expected numbers of suicides. Table 2 shows the result of this analysis. Because six comparisons were made, only p values of less than 0.05/6, or 0.0083, were considered statistically significant. On this basis, the number of actual suicides was significantly higher than that expected in each diagnostic subtype except for psychotic and nonpsychotic bipolar disorder. The standardized mortality ratios for psychotic and nonpsychotic subjects with major depression or bipolar disorder were not statistically different, as demonstrated by overlapping confidence intervals. The standardized mortality ratio for all nonpsychotic subjects was actually higher than that for psychotic subjects, but not significantly so.

DISCUSSION

Suicide in Psychotic Affective Disorder

We have demonstrated in a short-term follow-up study that major affective disorders are associated with a high risk of suicide but that this risk does not differ among patients rated as psychotic and nonpsychotic during their index hospitalizations. In contrast, Roose et al. (7) concluded that psychosis predisposes to suicide and that a delusional depressed patient is 5.3 times as likely to commit suicide as a nondelusional one. Their study subjects were all hospitalized patients, and the suicides occurred in the hospital. Our findings, on the other hand, were based on a 0–14-year follow-up of formerly hospitalized subjects. Only two subjects committed suicide in the hospital—both had bipolar affective disorder, and only one was psychotic.

Robins (13) recently reanalyzed psychological autopsy data on 134 subjects who had committed suicide in St. Louis during the 1950s. He reviewed the cases to determine the prevalence of psychosis and found that

TABLE 2. Observed and Expected Numbers of Suicides Among 1,593 Psychotic or Nonpsychotic Men and Women With Major Depression or Bipolar Disorder

Disorder	Suicides Observed			Suicides Expected	χ^2 (df=1)	Standardized Mortality Ratio	
	Men	Women	Total			Ratio	95% Confidence Interval
Major depression							
Psychotic	3	3	6	0.12	15.05[a]	50.00	18.25–108.83
Nonpsychotic	10	18	28	0.67	76.74[a]	41.79	27.76–60.39
Bipolar disorder							
Psychotic	2	0	2	0.19	3.31	10.50	1.18–37.91
Nonpsychotic	4	1	5	0.29	10.34	17.24	5.55–40.22
Total							
Psychotic	5	3	8	0.31	18.75[a]	25.81	11.23–50.86
Nonpsychotic	14	19	33	0.96	87.98[a]	34.38	23.65–48.28

[a]$p<0.001$.

25 (19%) of the patients were psychotic at the time of suicide. Among 63 subjects diagnosed as having affective disorder, 10 (15.9%) were psychotic. He concluded that approximately one suicide victim of five was psychotic and that over 80% of his sample were not "crazy" at the time of suicide. The results of the present study are in agreement. We, too, found that most (80.5%) of our patients with affective disorder who subsequently committed suicide were not psychotic. Furthermore, psychotic patients were not overrepresented among the 41 suicides that occurred in our follow-up. Although we did not conduct a psychological autopsy and cannot comment on the psychiatric status of the suicide victims at the time of death, psychotic affective disorder is generally stable diagnostically (14, 15). Thus, a person who is psychotic during one episode of illness is highly likely to be psychotic during subsequent episodes and, by inference, at the time of suicide as well.

Our results are also consistent with a recent report (16) on 23 delusional patients and 23 age-, sex-, and diagnosis-matched nondelusional control subjects who were followed over a 3-year period. Four psychotic patients and two nonpsychotic control subjects died, a nonsignificant difference. It is possible that a difference in suicide outcome would become evident in a longer follow-up. However, in a 30- to 40-year follow-up of delusional depressed patients, Coryell and Tsuang (17) found no significant difference in the suicide rates for psychotic and nonpsychotic patients with primary unipolar depression (8.4% versus 10.0%, respectively).

Do Bipolar Patients Have a Lower Suicide Risk?

It is worth noting that the percentages of deaths by suicide and the standardized mortality ratios of the bipolar patients in our study were lower than those found in the unipolar subjects. This suggests, although not conclusively, that bipolar patients may have a lower suicide rate, hence a lower risk for suicide. In our study, the lower rate of suicide in the bipolar subjects may be due to the proportion of manic subjects (74.7% of our bipolar sample at index admission), who have a low risk for suicide, while depressed bipolar patients have a suicide rate similar to that of unipolar patients (4). Taken together, these factors produced an unexpectedly low risk for suicide among the bipolar patients during the short-term follow-up.

Our finding of a lower suicide risk for bipolar patients is consistent with the results from two long-term follow-up studies of former inpatients (18, 19), a follow-up of outpatients (20), and a recent case-control study (21). A report by Tsuang (22), which demonstrated a significantly higher rate of suicide in relatives of unipolar probands than in relatives of bipolar probands, appears to support this finding. On the other hand, two studies (23, 24) have reported a higher suicide risk for bipolar patients than for unipolar patients, while four other studies (3, 25–27) reported similar risks in the two groups. Thus, the lack of concensus in the literature means that our findings must be viewed with caution.

Studies of suicide risk continue to be important because prevention of suicide is the ultimate goal of treatment. Future studies will need larger sample sizes and careful prospective assessment of relevant risk factors, including psychosis, to determine their relationship to suicide.

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Quantitative Magnetic Resonance Imaging and the Severity of Dementia in Alzheimer's Disease

William Bondareff, Ph.D., M.D., Janak Raval, M.D., Patrick M. Colletti, M.D., and Douglas L. Hauser, B.S.

The T_2 component of the magnetic resonance imaging (MRI) signal was measured in 11 brain loci in six elderly patients diagnosed as having probable Alzheimer's disease. T_2 values and relative amount of periventricular high-intensity foci were significantly correlated with dementia severity, indicated by the Blessed-Roth Dementia Scale score. Although the mean T_2 value for left hemispheric structures was more closely correlated with the dementia score, T_2 values did not differ significantly in the right and left hemispheres or in gray and white matter. These findings suggest that more severe dementia in Alzheimer's disease is associated with more water in the brain.

(Am J Psychiatry 1988; 145:853–856)

We report the results of a pilot magnetic resonance imaging (MRI) study of the relationship between T_2 relaxation time and the severity of dementia in six patients with probable Alzheimer's disease (1).

MRI depends on the broadcast of a signal generated by magnetized tissue components in response to an external radio frequency (2). The signal, which depends in part on T_1 and T_2 relaxation times, carries information reflecting tissue composition, in particular, the amount and distribution of free water (3). Besson et al. (4, 5) used a spin-lattice relaxation time method to study relationships between T_1 relaxation times in cerebral cortical white matter and the severity of dementia in Alzheimer's disease and related disorders. We chose not to use a spin-lattice relaxation time method because its need for at least two scanning sequences results in longer scanning times and an enhanced possibility for artifact related to subject movement. We chose, instead, to use a spin-spin relaxation technique and to measure T_2, the computation of which requires only a single scanning sequence. As our technique results in a T_2 map with adequate anatomical information, it appeared particularly well suited for use with demented patients, who are often unable to tolerate longer scanning.

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METHOD AND RESULTS

Six demented elderly patients were referred from the USC/St. Barnabas Alzheimer's Disease Diagnosis and Treatment Center with diagnoses of probable Alzheimer's disease (1). They had been thoroughly evaluated clinically, and the severity of their dementia had been measured with an extensive battery of neuropsychiatric tests, including the Mini-Mental State examination (6) and the Blessed-Roth Dementia Scale (7). The Mini-Mental State tests cognitive aspects of mental functioning and has been used extensively to define the severity of dementia. The Blessed-Roth Dementia Scale tests competence in personal, domestic, and social activities of daily living and has been extensively correlated with histological and biochemical changes associated with Alzheimer's disease. The six subjects all scored less than 3 on the instrument developed by Hachinski et al. (8) to differentiate dementias of vascular etiology from primary degenerative dementia.

Each subject underwent an MRI examination of the head with a Picker 0.5-tesla superconducting magnetic resonance imager; a head coil was used as a receiver. Axial images of the brain, 10 mm thick (without intervening gap), were obtained with a scanning technique that used a single pulse sequence/multi-echo (TE=40, 80 msec; TR=2250 msec) with a 256×256-pixel matrix and a 30-cm field of view. A T_2 map was calculated from which T_2 values for 2.3×2.3-mm regions of interest were obtained with the scanner's cursor. The scanning procedure required patients to be in the scanner for 9–10 minutes.

T_2 relaxation times were calculated from 11 brain loci: cingulate gyrus gray and white matter of the left and right hemispheres, posterior limb of the internal capsule bilaterally, gray and white matter of the fron-

TABLE 1. Neuropsychiatric Test Scores, MRI T_2 Relaxation Times From 11 Brain Loci, and Relative Amounts of Periventricular High-Intensity Lesions in Six Patients With Alzheimer's Disease

				T_2 Relaxation Time (msec)											
						Left Hemisphere									
								Cingulum				Frontal Lobe			
				Genu		Internal Capsule		White		Gray		White		Gray	
Patient	Age (years)	Mini-Mental State Score	Blessed-Roth Dementia Scale Score	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	80	10.0	13.0	70	0.7	122	10.6	70	8.5	63	2.1	61	5.7	63	2.1
2	68	11.5	1.5	67	0.7	61	1.4	54	0.7	62	4.9	54	4.2	59	7.9
3	75	21.0	2.0	64	1.4	66	3.5	66	5.7	62	1.4	70	2.1	64	9.2
4	75	22.0	1.0	53	4.9	59	2.8	51	4.2	62	6.4	51	2.1	63	4.9
5	80	24.0	3.5	67	0.7	79	3.5	62	0.0	73	10.6	98	9.9	66	1.4
6	83	30.0	0.0	47	2.1	58	0.0	51	0.0	59	8.5	49	0.7	56	2.1

tal lobe bilaterally, and genu of the corpus callosum (table 1). These brain loci, including both superficial and deep structures, were chosen because they were anatomically identifiable and provided regions of interest larger than 2.3×2.3 mm. Correlations between these values and the severity of dementia (Mini-Mental State and dementia scale scores) were tested with nonparametric, bivariate correlation analysis with Spearman rank-order correlation coefficients.

Although the sample was small (N=6), Spearman rank-order correlation coefficients suggested meaningful interrelationships, which are summarized in table 2. The Spearman coefficients for the correlations between Mini-Mental State score and T_2 values, although sometimes better than 0.5, showed no statistical significance ($p>0.05$). Spearman coefficients better than 0.8 were associated with correlations between dementia scale score and T_2 values that reached statistical significance in the genu, internal capsule bilaterally, gray and white matter of left cingulum and gray matter on the right, and white matter of the frontal lobe on the left (see table 2).

Mean left and right T_2 values were calculated from the T_2 values for internal capsule, cingulum, and frontal lobe cortex of the left and right hemispheres, respectively. The differences between the mean left and right hemispheric T_2 values were not significant. Both, like the T_2 value calculated from the midline genu, were correlated significantly with the dementia scale score; neither was correlated significantly with the Mini-Mental State score (table 3). Data from both hemispheres were therefore pooled, and a grand mean T_2 value was calculated from the 11 regions of interest. The correlation between this total mean T_2 value and the Mini-Mental State score was not significant; the correlation with the dementia scale score was highly significant ($r_s=0.9429$, N=11, $p=0.005$) (table 3).

Visual examination of the T_2-weighted (TR=2250 msec, TE=80 msec) and proton-density-weighted (TR=2250 msec, TE=40 msec) images indicated high-intensity periventricular lesions of varying size in each of the six brains studied. The proton-density- or T_2-weighted images that best demonstrated periventricular high-intensity foci were selected and photographically printed with a uniform 4× enlargement. The areas of photographic paper occupied by periventricular hyperintensity foci were cut out and weighed on an analytical balance. A ratio of the amount of periventricular lesion to the amount of cerebral hemisphere tissue was calculated for each patient. This ratio correlated significantly with the score on the dementia scale ($r_s=0.9000$, N=6, $p=0.043$) but not the Mini-Mental State ($r_s=-0.3000$, N=6, $p=0.5180$).

DISCUSSION

Tissue water content contributes to T_1 and T_2 relaxation times (9–13) and is directly related to the intensity of T_2-weighted images. Although the differential contributions of extracellular and intracellular water to T_2 values in brain are not known, high-intensity periventricular foci typically seen anterior and lateral to the frontal horns in T_2-weighted images have been found to have a microscopic structure consistent with increased interstitial (i.e., extracellular) water (14). These periventricular foci of hyperintensity, usually (but not always) insignificant in nondemented elderly subjects, were found in 10 of 12 patients with Alzheimer's disease studied by Fazekas et al. (14) and in all of the six patients with Alzheimer's disease we studied. While no correlation between periventricular foci of hyperintensity and severity of dementia was found by Fazekas et al. (14), we found a statistically significant correlation between the relative amount of hyperintensity lesion and the Blessed-Roth Dementia Scale score. It seems likely that the magnitude of relaxation times, which also correlated with the severity of dementia in our patients with Alzheimer's disease, as well as the extent of periventricular foci, reflect changes in tissue water, and, at least to some degree, they are influenced by changes in the extracellular compartment.

Our finding that T_2 values increase with the severity of dementia in Alzheimer's disease agrees with that of Besson et al. (4, 5), who found higher T_1 values in severely demented patients with Alzheimer's disease,

TABLE 1
(continued)

Right Hemisphere T_2 Relaxation Time (msec)										
Internal Capsule		Cingulum				Frontal Lobe				
		White		Gray		White		Gray		
Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Periventricular Lesions/ Cerebral Hemisphere Tissue
76	0.7	69	4.9	75	0.0	59	1.4	61	9.2	0.0399
66	1.4	66	0.0	59	0.7	59	0.7	61	1.4	0.0047
71	2.8	61	0.0	64	1.4	53	2.1	59	0.7	0.0389
68	4.2	—	—	58	0.7	51	0.7	55	3.5	0.0025
68	4.2	72	9.2	82	6.4	81	2.1	66	2.8	0.0862
62	4.2	48	4.2	52	4.2	52	0.0	58	2.1	0.0072

TABLE 2. Correlations Between MRI T_2 Values and Scores on the Mini-Mental State and Blessed-Roth Dementia Scale in Six Patients With Alzheimer's Disease

	Mini-Mental State		Blessed-Roth Dementia Scale	
Locus	r_s	p	r_s	p
Genu	−0.7537	0.084	0.8987	0.015
Left hemisphere				
Internal capsule	−0.6000	0.208	1.0000	0.0000
Cingulum				
White	−0.6667	0.148	0.9276	0.008
Gray	−0.3340	0.518	0.8804	0.021
Frontal lobe				
White	−0.2571	0.623	0.8286	0.042
Gray	−0.0580	0.913	0.6667	0.148
Right hemisphere				
Internal capsule	−0.6378	0.173	0.8117	0.049
Cingulum				
White	−0.4000	0.505	0.8000	0.104
Gray	−0.3714	0.469	0.9429	0.005
Frontal lobe				
White	−0.3889	0.538	0.6957	0.124
Gray	−0.2899	0.578	0.7537	0.084

TABLE 3. Correlations Between Scores on the Mini-Mental State and Blessed-Roth Dementia Scale and MRI T_2 Values for the Two Hemispheres Separately and Combined in Six Patients With Alzheimer's Disease

	Mini-Mental State		Blessed-Roth Dementia Scale	
Hemisphere	r_s	p	r_s	p
Left	−0.6000	0.208	1.0000	0.000
Right	−0.4286	0.397	0.8857	0.019
Left and right	−0.3714	0.469	0.9429	0.005

Parkinson's disease, or multi-infarct dementia than in nondemented control subjects. There were no significant differences among the three patient groups.

While it can be argued that T_2 values might reflect changes in the volume of CSF associated with atrophy of frontal cortex, cingulum, and genu of the corpus callosum, this is less likely with the T_2 measurement in internal capsule. That the latter, especially, correlated closely with the dementia scale score (table 2) supports our suggestion that the regional differences we report in the relationship between T_2 values and the dementia scale score reflect differences in the distribution of free water. They are consonant with the results of quantitative computerized tomographic (CT) studies of demented elderly patients, which showed attenuated CT numbers in selective but different parts of the brain (i.e., anterior frontal lobe, medial temporal lobe, and head of caudate nucleus) (15).

Our findings, in general, are comparable to those of Besson et al. (4) in that they imply bilateral pathology and suggest that it might be more prominent in the left than in the right hemisphere. Of the five brain loci examined in both the right and left hemispheres (gray and white matter in cingulate and frontal lobes and the internal capsule), Spearman correlation coefficients associated with left hemisphere structures were greater in three (table 2). The mean Spearman coefficient associated with left hemispheric structures was greater than that associated with right hemispheric structures (table 3). Nonetheless, our data seem more consonant with a generalized T_2 enhancement, involving both the right and left cerebral hemispheres to approximately the same degree. In support of a nonregional enhancement of T_2 values, Wilcoxon two-sample tests (with a continuity correction of 0.5) showed the T_2 value for each of the five loci examined in the left hemisphere not to differ significantly from the corresponding value in the right hemisphere. Because there was no significant difference between the T_2 values of the left and right hemisphere structures or between gray and white matter, a cerebral-wide mean T_2 value appears to be more representative of the whole than any single region. Such a value is readily calculated.

A grand mean T_2 value was calculated from the 11 regional T_2 values already derived. Spearman correlation coefficients showed a highly significant correlation between this grand mean T_2 value and the dementia scale score; the correlation with the Mini-Mental State value was, predictably, not significant. This mean T_2 value, as well as the relative amount of periventricular lesion, may provide an in vivo estimate of brain water that correlates directly with the severity of dementia in

Alzheimer's disease as indicated by the score on the Blessed-Roth Dementia Scale.

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Reliability of Psychiatric Scales in Patients With Dementia of the Alzheimer Type

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For 43 patients with probable Alzheimer's disease who were screened for psychiatric disorders, the interrater reliability of the Global Deterioration Scale, BPRS, and Hamilton Rating Scale for Depression was high (intraclass correlation, 0.82–0.998). As expected, the prevalence of psychiatric symptoms in this sample was low. The score on the Zung Self-Rating Depression Scale correlated with the score on the rater-administered Hamilton depression scale in patients whose Alzheimer's disease was of low severity (N=24) but not high severity (N=19).

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Advancing the study of brain and behavior in dementia of the Alzheimer type requires integration of neuropsychological and neuroimaging data on regional brain anatomy and physiology with measures of clinical status. The diagnosis of Alzheimer's disease antemortem is based on clinical presentation and excludes other neurologic and psychiatric disorders. However, psychiatric symptoms have been associated with the progression of Alzheimer's disease (1–4). The base rate of psychiatric symptoms in patients with Alzheimer's disease who are screened for concomitant psychiatric disease is unknown.

As part of our ongoing research on regional brain dysfunction and behavior in dementia of the Alzheimer type, we found it necessary to examine the feasibility of using standard rating scales for staging the disease and quantifying psychiatric symptoms. The Global Deterioration Scale (5) describes the phenomenology of Alzheimer's disease and has been used to quantify its progressive course. However, its interrater reliability has not been established. The Brief Psychiatric Rating Scale (BPRS) (6) and the Hamilton Rating Scale for Depression (7) have shown, respectively, interrater reliability in samples of schizophrenic and depressed patients. To our knowledge, their reliability for patients with Alzheimer's disease has not been examined. Neither instrument was designed for use with demented patients. However, numerous clinical trials of treatment for the psychiatric symptoms of demented patients have applied these scales (8, 9).

We also evaluated the validity of the Zung Self-Rating Depression Scale (10) by comparing it with objective clinical ratings. Such self-rating scales, if valid, could enable more frequent evaluations of changes in depressive symptoms. However, it is likely that with advanced Alzheimer's disease, patients lose the intellectual capacity and insight to provide valid responses to self-rating scales.

In the present report we describe 1) the interrater reliability for the Global Deterioration Scale, the BPRS, and the Hamilton depression scale in a sample of patients with probable Alzheimer's disease who were screened for psychiatric disease, 2) the base rate of psychiatric symptoms in these patients as a function of disease severity, and 3) the correlation between objective clinical ratings and self-report measures of depression in patients with low and high severity of Alzheimer's disease.

METHOD

Data were collected on 43 (14 male and 29 female) consecutively referred ambulatory patients who met the NINCDS/ADRDA criteria for probable dementia of the Alzheimer type (11). The age range was 55–88 years (mean±SD=72.80±7.25), and the education range was 4–18 years (mean±SD=11.93±3.56). Standard clinical and laboratory evaluations excluded patients with evidence of other psychiatric, medical, or neurological disorder.

Structured mental status examination (12), assessment of disease stage with the Global Deterioration Scale, and completion of the Hamilton scale and BPRS were performed independently by two of the authors (G.L.G. and R.E.G.) within 1 week. At least one family member provided the patient's history. The Zung scale was completed by the patient at the time of evaluation.

Limited adaptation of the observer's ratings was re-

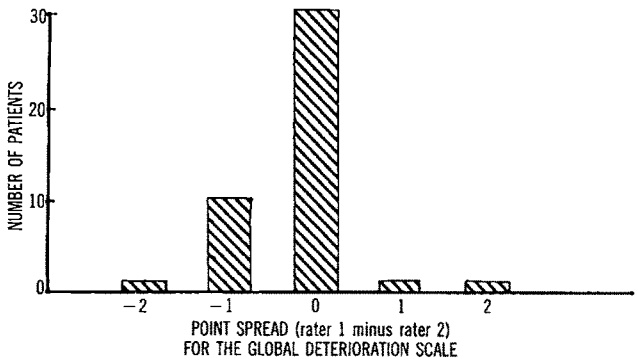
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FIGURE 1. Agreement of Two Raters on Global Deterioration Scale Scores of 43 Patients With Alzheimer's Disease



quired. For example, the "work and activities" item on the Hamilton scale was rated in the context of disease-related functional limitations as assessed with standard measures of geriatric function (i.e., activities of daily living and instrumental activities of daily living) (13).

The Global Deterioration Scale is a 7-point Likert-type scale. The Hamilton scale, BPRS, and Zung scale yield summary scores that quantify the degree of severity. Interrater reliability was assessed with the intraclass correlation procedures described by Fleiss (14) and implemented with the BMDP statistical software (15). The average of the two Global Deterioration Scale scores was used to classify the severity of each patient's dementia as low (Global Deterioration Scale stage 3 or 4, N=24) or high (stage 5 or higher, N=19) to examine the effect of severity on the relations among the psychiatric scales. The two patient groups were similar in age (low severity=72.63±8.70 years, high severity=73.37±5.10) and education (12.30±3.71 and 11.44±3.50 years, respectively).

RESULTS

The intraclass correlation between the two raters for the Global Deterioration Scale was 0.82. There was a significant case effect ($F=5.53$, $df=1, 42$, $p<0.001$) and rater effect ($F=4.62$, $df=1, 42$, $p<0.05$). Figure 1 shows the point spread frequency distribution, which indicates that the two raters were within one point for 41 of the 43 cases.

For the BPRS and Hamilton ratings the intraclass correlations were 0.997 and 0.998, respectively, with significant case effects (BPRS: $F=134.33$, Hamilton: $F=441.73$, $p<0.001$ for both) and no rater effects ($F<1$ for both) (figure 2).

Low levels of psychopathology were evident. To examine the effects of Alzheimer's disease severity on psychiatric symptoms, the division of patients into severity groups was entered as a between-group factor in an analysis of variance (ANOVA), with scale (BPRS, Hamilton, or Zung) as a within-group factor. There was a significant Severity by Scale interaction ($F=5.82$, $df=2, 40$, $p<0.01$). This interaction is illustrated in figure 3. The mean±SD BPRS score was higher in the group with more severe Alzheimer's disease—low severity=21.88±4.40 (range=18–39), high severity=26.26±9.36 (range=19–55) ($t=-2.03$, $df=42$, $p<0.05$). The severity groups did not differ in their scores on the Hamilton or Zung scale—Hamilton: low severity=3.25±6.07 (range=0–28), high severity=2.42±3.04 (range=0–10) ($t<1$); Zung: low severity=36.61±8.05 (range=23–55), high severity=39.00±8.55 (range=21–54) ($t<1$).

FIGURE 2. Agreement of Two Raters on BPRS and Hamilton Depression Scale Scores of 43 Patients With Alzheimer's Disease

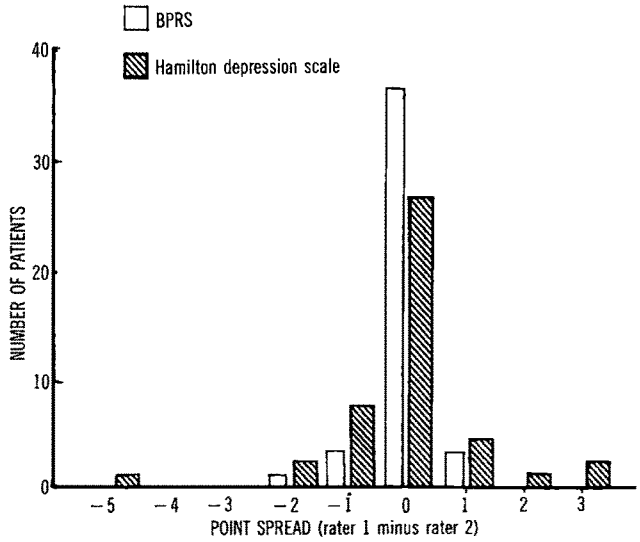
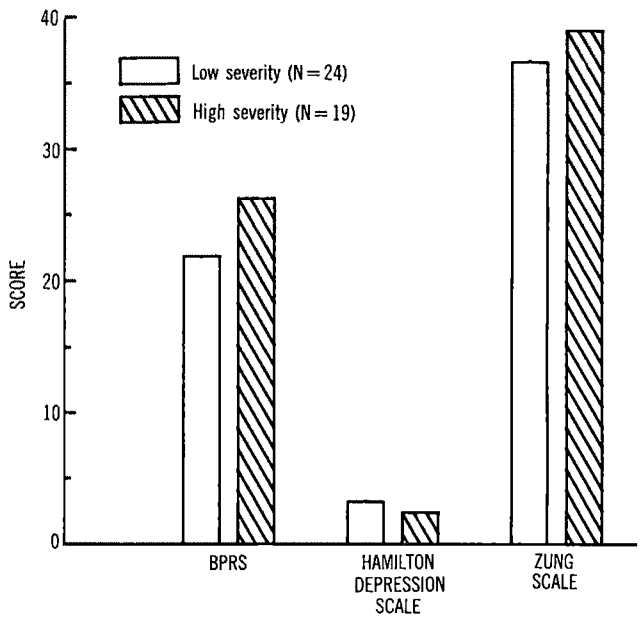


FIGURE 3. Mean Scores on BPRS, Hamilton Depression Scale, and Zung Scale of Patients With Alzheimer's Disease of Low or High Severity



We evaluated the relationships among the behavioral measures within each severity group separately. For the low-severity patients, the BPRS score correlated well with the Hamilton score ($r=0.89$, $df=22$, $p<0.01$) and the Zung score ($r=0.50$, $df=22$, $p<0.01$). The Hamilton score also correlated with the Zung score in this group ($r=0.49$, $df=22$, $p<0.01$). For the high-severity group, the correlation between the two rater-administered scales, the BPRS and Hamilton scale, remained significant ($r=0.57$, $df=17$, $p<0.01$). However, there was no correlation between scores on either of the rater-administered scales and the Zung self-report ($r=-0.13$ and 0.01, $df=17$, n.s., for the BPRS and the Hamilton scale, respectively). The correlations between these ratings and the Zung score were significantly lower for the high-severity group than for the low-severity group (BPRS: $Z=2.21$, Hamilton scale: $Z=1.71$, $p<0.05$ for both).

DISCUSSION

The present results suggest that psychiatric symptoms can be assessed reliably with objective rating scales in patients with probable dementia of the Alzheimer type. In our study reliability was maintained both for mildly to moderately demented patients and for highly impaired patients. It should be noted that this reliability of the clinical instruments was achieved with frequent interrater reliability sessions and patient evaluations separated by no more than 1 week. The interrater reliability for the Global Deterioration Scale is especially important since it frequently provides the basis for patient classification and documentation of disease stage in research and in clinical trials of interventions.

The low overall level of psychopathology observed in our sample was obtained probably because we excluded patients with histories of significant psychiatric disorder. Similarly, patients who required acute psychiatric intervention at the time of initial presentation were excluded.

Our finding of a low frequency of depressive symptoms contrasts with the findings of Reifler et al. (2) and Miller (3) but is consistent with those of Knesevich et al. (4). Only the latter study had a sample as homogeneous as ours, albeit with mild dementia only. Reifler et al. (2) found that the prevalence of depression decreased with the increase in severity of dementia. In contrast, we found no difference in measures of depressive symptoms when mildly to moderately impaired patients were compared to patients with moderate to severe Alzheimer's disease. Notably, Reifler et al. (2) estimated that only 71% of their demented sample were suffering from Alzheimer's disease. Perhaps other dementias (e.g., multi-infarct dementia) are associated with more psychopathology, including depression.

In recently published articles, Lazarus et al. (16) and Merriam et al. (17) reported high prevalences of depression in homogeneous samples of patients with Alzheimer's disease. Unlike the present investigation, these studies did not exclude patients who had major depressive disorder at the time of evaluation or patients with previous histories of depression.

The objective clinical ratings correlated with self-ratings of depression only for the less impaired group. Thus, investigation of depression in advanced Alzheimer's disease with self-report measures is of questionable utility. The lack of correlation for the more severely impaired group may be related to poorer insight. On the other hand, while all patients were able to complete the Zung scale, perhaps diminished ability to comprehend its content made this instrument less useful for the more severely demented patients.

It should be recognized that the Hamilton depression scale, BPRS, and Zung scale were not designed to evaluate patients with dementia. However, the quantification of psychiatric symptoms is always made in the context of baseline function and coexisting disorders. Therefore, these scales can be useful in studies comparing behavioral disorder in dementia with psychiatric disorders, such as major depression in the elderly, schizophrenia in older age, and late-life paranoid disorders. This strategy is likely to contribute to the understanding of relationships between brain function and behavior in multiple disorders.

Miller's study (3) examined measures of depressive symptoms in patients with presumed Alzheimer's disease and yielded high correlations between Hamilton scores and self-reports of depression. Indeed, these correlations appeared higher in demented patients than in elderly depressed patients. Her findings are consistent with our results for the less impaired group. Miller did not stratify her "organic group" by degree of severity of impairment. Patients with focal neurological signs and those with past histories of cerebrovascular disease were excluded, but her study antedated the more rigorous criteria (including CAT scan of the brain) outlined by the NINCDS/ADRDA task force (11).

We have demonstrated that measures of disease severity and concomitant psychopathology in a homogeneous sample of patients with Alzheimer's disease can be administered reliably. This reliability will enable consistency in longitudinal research and the evaluation of intervention strategies. Such behavioral measures can provide the basis for relating clinical data on patients with Alzheimer's disease to neuroimaging and neuropsychological data.

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Alpha Frequency in Schizophrenia: An Association With Enlarged Cerebral Ventricles

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Low alpha frequency (less than 10.2 Hz) occurred more frequently in medication-free schizophrenic patients than in normal control subjects, as determined by quantitative EEG analysis. Furthermore, those patients with low alpha frequency had significantly larger lateral ventricles, as measured by CT scan, than did other schizophrenic patients (mean±SD ventricle-brain ratios=9.8±1.9 versus 5.0±2.4; p<0.01). This finding suggests the existence of a relationship between cerebral structural pathology and the alpha rhythm that may be based on involvement of alpha-generating structures which border the cerebral ventricles. Future EEG studies of schizophrenia may resolve these questions in the context of other brain findings.

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The thalamus and vision-related cortex (optic radiations and occipital lobe) have been implicated as the brain structures involved in the generation of alpha rhythm (1–3). The thalamus forms part of the inferior border of the lateral ventricles and the superior border of the third ventricle (4), while the vision-related cortex surrounds the posterior aspects of the lateral ventricles including the posterior horns (4).

In schizophrenia, enlargement of the lateral and third ventricles has been reported (5–8), as has low alpha frequency (9–12). Moreover, there is evidence from one recent study using MRI that the greatest degree of cerebral ventricle enlargement in schizophrenic patients occurs over the thalamus (13). Together, these data raise the possibility that in schizophrenia, low alpha frequency is associated with ventricle enlargement, an association that may be based on the involvement of the brain structures which generate alpha. This study was undertaken to examine this question through the use of computerized EEG techniques and CT.

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METHOD

The subjects were 16 psychiatric inpatients (13 men and three women) with chronic schizophrenia (*DSM-III*). The mean±SD age of the group was 30±5 years. All patients had their EEG recorded during a period of medication withdrawal of at least 4 weeks. All but one were right-handed. Eleven of these patients were also studied after they had received a stable dose of neuroleptics for at least 4 weeks. In nine subjects the medication was oral haloperidol, 0.4 mg/kg per day. The medications for the other two patients were oral prolixin, 20 mg/day, and haloperidol decanoate, 50 mg i.m. every other week, respectively.

Four additional patients, ranging in age from 25 to 30 years, were examined. Two men and one woman had diagnoses of atypical psychosis, mixed substance abuse, and mixed personality disorder. A 30-year-old male subject had the diagnosis of schizophrenia complicated by chronic substance abuse, which was ongoing during his hospitalization. As with the schizophrenic patients, these patients had histories of extensive neuroleptic treatment and had been withdrawn from neuroleptics for at least 4 weeks at the time of their EEG recording.

Eight paid volunteers and 13 members of the clinical and research staff of the William A. White Building served as normal control subjects. The mean±SD age of the group, which included 15 men and six women, was 31±7 years. Seventeen were right-handed and four were left-handed. All patients and control subjects provided written informed consent.

The methods for recording EEGs and performing power spectral analysis and the differences in power between the patients with schizophrenia and control subjects have been described elsewhere (14, 15). The subjects were seated comfortably in a darkened, soundproof room. Twenty-eight electrodes were applied to the scalp, by standard methods according to the International 10–20 system, and were referenced to linked ears. The eight additional electrode placements were at FC5, FC6, CP5, CP6, CP1, CP2, PO1, and PO2, points corresponding to the 5% and 10% lines interpolated in the 10–20 system. Filter settings were at 1 Hz and 70 Hz, with the 60 Hz filter at the "in" position. Horizontal eye movements were read on a separate channel by recording the potential between

electrodes placed at the outer canthus of each eye. Filter settings for this amplifier were at 0.1 Hz and 70 Hz.

Record contaminated by blinks was deleted automatically and by visual inspection, while record contaminated by horizontal eye or facial muscle movement artifact was deleted by visual inspection alone. Power spectrum analysis was then performed on the remaining EEG record, and a plot of amplitude (square root of power) versus frequency for each lead was generated for each subject.

The presence or absence of an alpha peak was determined by visual inspection of the frequency plots and an amplitude cutoff of 2.5 μV. If the subject's alpha amplitude was below 2.5 μV, he or she was classified as having no significant alpha activity. For those subjects with significant alpha activity, dominant alpha frequency was determined on the left-sided and midline electrode locations by ascertaining the scalp location of maximum alpha voltage and then taking the frequency at this location. Those subjects with a dominant frequency in the alpha band below 10.2 Hz were classified as having low alpha frequency. This cutoff was derived from a topographic EEG study of 16 normal control subjects (16).

Since alpha activity is greatly enhanced by eye closure, the determination of dominant alpha frequency was made while the subjects' eyes were closed. Obviously, sufficient artifact-free EEGs were obtained from all of the subjects with the eyes closed. To facilitate this, gauze was taped gently over the eyes during recording to diminish eye movement. The mean±SD number of artifact-free EEG epochs (2.56 seconds/epoch) obtained for the patients was 32±26 (over 1 minute), compared with 64±37 (over 2.5 minutes) for the normal control subjects.

CT scans were obtained on each schizophrenic patient with a GE 9800 scanner. Cerebral ventricle size, as reflected by the ventricle-brain ratio (VBR), was determined by the planiometric technique described by Weinberger et al. (6, 8). Estimates of frontal atrophy and third ventricle size were also obtained (8). Scans were not obtained on normal control subjects.

Results are reported as mean±SD.

RESULTS

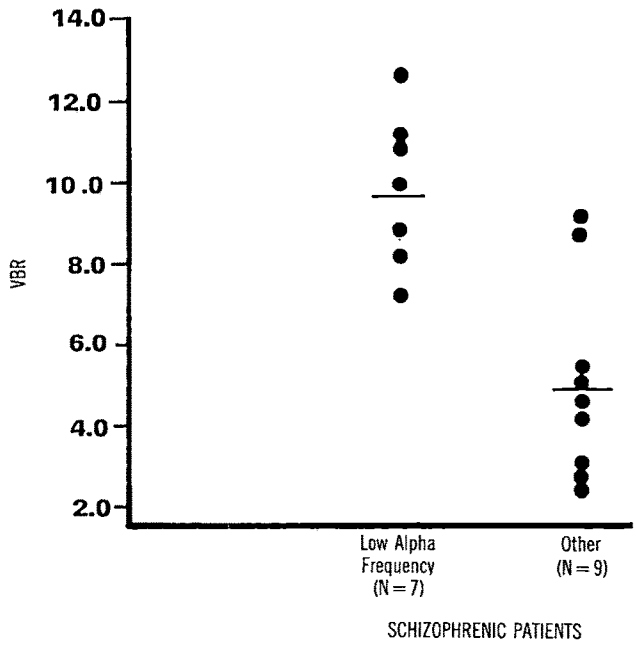
Seven schizophrenic patients (one woman and six men; mean age was 29±5 years and was not different from that of the remaining schizophrenic patients) had low alpha frequency. One patient had an alpha frequency above 10.2 Hz. Of the normal subjects, only five had low alpha frequency, while 13 had an alpha frequency above 10.2 Hz ($p=0.009$, Fisher's exact test [17]). The mean alpha frequency for the eight schizophrenic patients with a dominant frequency in the alpha range was 9.77±0.81 Hz, compared with 10.72 ±0.68 Hz for the normal subjects ($U=23$, $p<0.01$, Mann-Whitney U test [17]). Six schizophrenic patients and three normal subjects had no dominant alpha frequency. Two schizophrenic patients had two dominant frequencies, one above and one below 10.2 Hz. Hence, 13 of 21 normal control subjects (62%) had a dominant alpha frequency above 10.2 Hz, compared to only 1 of 16 patients with schizophrenia (6%) ($p<0.001$, Fisher's exact test). Low alpha frequency did not occur in the three nonschizophrenic patients.

Of the normal subjects with alpha activity (N=18), the highest voltage occurred at PO1 in eight subjects, O1 in six subjects, and various other locations in four subjects. Of the patients with schizophrenia, the peak voltage location was O1 for three subjects, PO1 for one other, PZ in two subjects, and at two electrode locations in the four remaining subjects (PO1 or O1 was one of the two leads for these subjects).

The mean VBR of the schizophrenic patients with low alpha frequency was larger than that of the other schizophrenic patients (figure 1). Alpha frequency correlated with VBR in the schizophrenic patients who had a single dominant alpha frequency ($r_s=-0.70$, $N=8$, $p\leq0.05$). In the group of schizophrenic patients who did not have low alpha frequency, six patients with no significant alpha had a mean VBR of 4.47±2.38. The single patient with a dominant frequency above 10.2 Hz had a VBR of 4.57, and the VBRs of two individuals with dominant alpha frequencies above and below 10.2 Hz were 4.98 and 8.82, respectively.

In contrast, there were no significant differences between the schizophrenic patients with low alpha fre-

FIGURE 1. VBRs of Schizophrenic Patients With Low Alpha Frequency and of Other Schizophrenic Patients[a]



[a]The mean±SD VBR of the patients with low alpha frequency (9.8±1.9) was significantly greater than that of the other schizophrenic patients (5.0±2.4) ($U=6$, $p<0.01$).

quency and the other schizophrenic patients in either third ventricle size (mean VBR=1.3±0.7 versus 1.1±0.4; U=25, p<0.4) or frontal atrophy (mean atrophy score=1.2±0.6 versus 0.9±0.4; U=20, p<0.3). Weak trends were observed for the correlations between alpha frequency and third ventricle size ($r_s=-0.57$, N=8, p<0.15) and frontal atrophy scores ($r_s=-0.61$, N=8, p<0.15).

Three of the 11 patients who were also recorded during neuroleptic treatment did not have a dominant alpha frequency while medication free. During neuroleptic treatment two of these patients had alpha activity. In the remaining eight patients, neuroleptic treatment lowered the mean alpha frequency from 9.76 to 9.22 Hz (t=1.12, df=7, p<0.15, paired t test). The two largest VBRs (12.58 and 11.14) of the entire patient group were obtained in two subjects in whom neuroleptics did not lower alpha frequency.

There were no significant correlations between alpha power, measured while the subjects' eyes were closed, and any of the three variables derived from the CT scan.

DISCUSSION

As a group, the schizophrenic patients with low-frequency alpha activity (44%, compared with only 24% of the normal control subjects) had a significantly greater degree of cerebral ventricle enlargement than other schizophrenic patients. Previous work (1, 2) suggests that the thalamus is involved with alpha generation. In addition, the thalamus constitutes a portion of the lower margin of the cerebral ventricle (4), the area over which the greatest degree of ventricle enlargement may occur in schizophrenia (13). Taken together, this evidence makes it tempting to speculate that there are neuropathological processes in schizophrenia which involve the thalamus and may also be responsible for the low-frequency alpha often seen in this disorder. Third ventricle enlargement, however, was not associated with low alpha frequency. Because the borders of the superior part of the third ventricle are also determined by the thalamus, a hypothetical relationship between reduced thalamic volume and low alpha frequency may prove difficult to substantiate.

In this study, neuroleptics lowered alpha frequency in patients with relatively normal VBRs. This evidence, coupled with a previous report in which neuroleptic treatment increased the amount of low-frequency alpha (18), suggests that the low alpha frequency might be explained by persistent neuroleptic concentrations in the CNS of the schizophrenic patients, despite the prolonged period of medication withdrawal. Two lines of evidence argue against this: 1) the failure of neuroleptics to slow alpha in the two patients with the largest VBRs who also had low alpha frequencies and 2) the absence of lowered alpha frequency in three nonschizophrenic patients with histories of extensive neuroleptic treatment.

One other issue is whether the low-frequency alpha activity could be related to an excess of undetected horizontal eye movement in the patients. Although we believe our artifact rejection methods are adequate, we decided to examine the effect of both horizontal eye movements and blinks on dominant alpha frequency in a group of nine normal control subjects. We found that the dominant frequency in these normal subjects significantly increased before either type of eye movement. This indicates that when our artifact removal strategy is used, populations with increased eye movement might be expected to have an increase in the dominant frequency, in contrast to the low alpha frequency found in schizophrenic patients.

At any rate, given the preliminary nature of this study, particularly the small sample size and the complexities of sorting out the confounding effects of previous neuroleptic treatment, these and other questions should be resolved through future studies that use both CT and MRI and a population of subjects who have never received neuroleptic medication.

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Combat-Related Posttraumatic Stress Disorder Among Second-Generation Holocaust Survivors: Preliminary Findings

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The authors assessed the impact of the Nazi Holocaust on the course and symptoms of posttraumatic stress disorder (PTSD) among Israeli combat stress reaction casualties. They examined a sample of 96 such casualties of the 1982 Lebanon War whose parents had gone through the Nazi Holocaust and compared them to casualties who did not have such family history for 3 consecutive years beginning 1 year after their participation in the war. Results showed that 2 and 3 years after their participation in the 1982 Lebanon War, the children of Holocaust survivors, i.e., "second-generation" casualties, had higher rates of PTSD than did the control subjects, as well as a somewhat different clinical picture. Clinical and methodological implications of the findings are discussed.

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Participation in combat has been found to have pathogenic effects (1, 2). During battle, the stress of war may result in combat stress reaction, also known as "battle shock," which is defined as a breakdown in a soldier's ability to function according to prescribed military procedures. At the end of the Lebanon War, the most common psychiatric disorder among Israeli soldiers with combat stress reaction was posttraumatic stress disorder (PTSD) (3). The characteristic symptoms of PTSD involve reexperiencing the traumatic event, numbing of responsiveness to or reduced involvement with the external world, and a variety of autonomic, dysphoric, or cognitive symptoms.

Numerous factors may affect the perpetuation of PTSD in combat stress reaction casualties; among them are prior experiences that may render an individual more susceptible to the detrimental impact of such an episode. One such prior experience may be having parents or family members who survived the Nazi Holocaust.

Psychiatric literature (4–7) argues that the Holocaust has had a long enduring detrimental impact on the survivors and their children. Research has shown that Holocaust survivors suffer from PTSD as a result of their experience and that their children suffer from similar symptoms at a lower intensity. The transgenerational effects observed in children of survivors can be regarded as "secondary traumatization," a term coined by Rosenheck and Nathan (8) to describe similar effects they observed in children of fathers with combat-related PTSD.

Danieli (6) reports that Holocaust survivors' children often react with severe psychopathological responses (i.e., anxiety) when exposed to stress. According to Barocas and Barocas (9), children of survivors suffer from high vulnerability, a condition that undermines narcissistic defenses; Shaw (10, 11) has pointed out that such defenses shield combatants from feelings of helplessness and fear of death, which are among the main causes of PTSD.

One of the most salient characteristics of Holocaust survivors and their offspring is the feeling of survival guilt—the feeling that they do not quite have the right to live when so many others were killed (4). The conflict between the desire to live and the guilt-ridden approbation of that desire then experienced by the Holocaust survivors' offspring who are later engaged in combat would exacerbate survival guilt—also one of the main symptoms of PTSD (2).

Conflicts about the expression of aggression have also been found to be strong in children of survivors. On the one hand, aggression by their children is encouraged by Holocaust survivors, who often vent their anger on their offspring (12) or unconsciously push them to act out the aggression that they themselves had not been able to express (13); on the other hand, survivors and their children have a profound fear of being aggressors and a great need to justify any aggression as temporary and purely defensive (14). The tension in combat between the opportunity for the release of aggression and the internalized prohibition against killing is common to all soldiers and would seem to be intensified in Holocaust survivors' offspring because it

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duplicates a tension that has been present in their upbringing.

Some studies (15) contend that Holocaust survivors and their children do not manifest serious psychological impairments. One of the many difficulties in arriving at a clear assessment is that almost all of the studies to date have been based on clinical impressions of a limited number of individuals in treatment. To our knowledge, few researchers have examined an adequate control group, and none have used a longitudinal design.

In the present study, we focused on the course of PTSD among second-generation Holocaust survivors and control subjects, employing a longitudinal design and assessing a relatively large sample of individuals who, until the 1982 Lebanon War, had not shown any overt manifestations of psychological disorder. We predicted that among combatants with an antecedent combat stress reaction syndrome, those whose parents survived the Holocaust would exhibit higher rates of combat-related PTSD than comparable combatants without such a family history.

METHOD

The subjects were obtained from the population of soldiers who fought on the front line during the Lebanon War (1982) and who were identified by Israel Defense Forces mental health personnel as combat stress reaction casualties. For the purpose of this study, we define combat stress reaction as the behavior of a soldier which indicates that the soldier has ceased to function as a combatant.

Our subjects showed neither indications of serious physical injury nor indications of other combat-related disorders, such as brief reactive psychosis or factitious disorders. In addition, since the research examined the impact of parents' experiences in Nazi concentration camps in Europe during World War II, only subjects whose parents were of European descent were included in the study.

Ninety-six soldiers participated in the study at three points in time. The subjects were divided into two groups according to whether at least one of their parents was a Holocaust survivor; 44 subjects were offspring of survivors (second generation) and 52 were not (not second generation).

Of the 96 subjects, 60 (62.5%) ranged in age from 18 to 33 years, and 36 (37.5%) were above age 33 (median age, 27 years). Seventy-nine (82.3%) were married. Eleven (11.5%) of the subjects had completed eighth grade, 23 (24.0%) had had at least some high school, 34 (35.4%) had completed high school, and 28 (29.2%) had studied beyond high school; 33 (34.4%) were draftees doing their 3 years of mandatory military service, and 63 (65.6%) were reserve soldiers.

Data retrieved from official military records indicate that this sample did not differ significantly from our original sample of 382 Israeli soldiers who had combat stress reaction during the Lebanon War (3) with respect to their sociodemographic and military backgrounds. Chi-square tests indicated that the two groups did not differ significantly with respect to any sociodemographic or military variable.

The PTSD inventory (given to subjects 1, 2, and 3 years after participation in the war) consists of 13 statements describing the *DSM-III* symptoms of PTSD as adapted for war trauma (3). The respondent was asked to indicate whether he had experienced each of the symptoms within the past month. The 13 statements were divided into three categories of symptoms corresponding to the following three *DSM-III* criteria for the diagnosis of PTSD: 1) reexperiencing of the trauma (three statements), 2) numbing of responsiveness to or reduced involvement with the external world (three statements), and 3) additional symptoms not present before the trauma (seven statements). A soldier was considered to suffer from PTSD when he reported at least one of the symptoms in each of categories 1 and 2 and at least two symptoms from category 3. (For detailed information about reliability and concurrent validity of the PTSD inventory, see Solomon et al. [3].)

Since differences in PTSD between the two groups of soldiers may be due to prewar differences, we assessed the soldiers' premilitary adjustment. This index was a composite score of intelligence, social performance, and personality features used by the Israel Defense Forces for assignment of soldiers to military units and prediction of subsequent functioning. The scores were obtained by a structured interview conducted by a specially trained interviewer when soldiers were first drafted at age 18.

Approximately 1, 2, and 3 years after their participation in the war, the subjects were asked to report to the headquarters of the Surgeon General of the Israel Defense Forces. The subjects received a personal letter explaining that they had been randomly selected to participate in a routine, periodical health assessment conducted as part of the Medical Corps' concern for the well-being of its regular and reserve soldiers. The soldiers were assured that the data would remain confidential and would in no way affect their status in military or civilian life. The subjects were seated in groups of seven to 19, where they individually filled out the battery of questionnaires.

Although secondary gain considerations may have led subjects to overly endorse emotional reactions, they were clearly informed that no military health profile would be changed on the basis of their reports. Moreover, subjects were aware that a different administrative unit was responsible for claims for physical or mental injuries.

RESULTS

A two-way analysis of variance (ANOVA) for categorical data performed on the rate of PTSD diagnosis by study group and time of measurement (as a re-

TABLE 1. PTSD Symptoms Among Soldiers With Combat Stress Reaction Who Were or Were Not Offspring of Holocaust Survivors

Group and Time After Lebanon War	Rate of PTSD (%)	Number of Symptoms		PTSD Inventory Scores[a]									
				Intrusiveness		Emotional Numbing		Hyper-alertness		Cognitive Impairment		Guilt Feelings	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Second-generation soldiers (N=44)													
First year	70	7.59	3.03	0.73	0.30	0.48	0.36	0.71	0.38	0.64	0.48	0.23	0.33
Second year	73	7.00	3.02	0.69	0.33	0.44	0.31	0.67	0.41	0.52	0.51	0.18	0.29
Third year	64	6.59	3.93	0.61	0.36	0.41	0.35	0.60	0.42	0.57	0.50	0.23	0.33
Not-second-generation soldiers (N=52)													
First year	60	6.07	3.92	0.57	0.40	0.42	0.37	0.55	0.39	0.51	0.50	0.17	0.31
Second year	52	5.83	3.80	0.55	0.40	0.40	0.37	0.56	0.40	0.47	0.50	0.16	0.32
Third year	39	4.04	3.86	0.39	0.40	0.26	0.35	0.35	0.38	0.34	0.48	0.15	0.33

[a]Scores ranged from 0 to 1.

peated factor) yielded significant main effects for time ($\chi^2=14.94$, df=2, $p<0.01$) and study group ($\chi^2=6.70$, df=1, $p<0.05$). As can be seen in table 1, the percent of soldiers diagnosed as having PTSD decreased over time. Additionally, a higher PTSD rate was found among second-generation than among not-second-generation subjects.

Although the ANOVA yielded a nonsignificant interaction between time and second generation, the decrease in the PTSD rate over time was steeper among not-second-generation than among second-generation casualties (table 1). The higher rate of PTSD among second-generation casualties was more salient at 3 years than at 1 year after the war.

A two-way ANOVA for group and time (as a repeated measure) performed on the number of symptoms reported as present yielded significant main effects for time ($F=12.87$, df=2, 180, $p<0.01$) and study group ($F=6.99$, df=1, 90, $p<0.05$). A post hoc Scheffe test for repeated measures ($\alpha=0.05$) revealed that the mean±SD number of symptoms reported as present was higher 1 and 2 years after the war (6.74±3.62 and 6.35±3.51, respectively) than at 3 years after the war (5.16±4.08). In addition, second-generation casualties reported more mean±SD PTSD symptoms (7.06±3.36) than not-second-generation casualties (5.31±3.94).

The ANOVA indicated that the time interaction approached significance ($F=2.45$, df=2, 180, $p<0.10$). A test for simple main effects (16) revealed that second-generation casualties reported more PTSD symptoms than not-second-generation casualties only at 3 years after the war. Additionally, the number of reported symptoms decreased over time only among not-second-generation subjects.

Analysis of covariance indicated that the difference between second-generation and not-second-generation groups on the number of PTSD symptoms reached significance after controlling for age, education, family status, and prewar adjustment. An additional ANOVA yielded no significant differences in prewar adjustment between the two study groups. These findings imply that group differences in PTSD do not depend on sociodemographic variables or on prewar adjustment.

Adopting Laufer et al.'s (17) four criteria for PTSD, we assigned the 13 statements from the PTSD inventory to each criteria: 1) intrusiveness (three statements); 2) emotional numbing (three statements); 3) hyperalertness (three statements); and 4) cognitive impairment (two statements). The two remaining statements related to guilt feelings.

The two-way ANOVAs yielded a significantly higher reported occurrence of intrusiveness ($F=7.26$, df=1, 90, $p<0.01$) and hyperalertness ($F=6.02$, df=1, 90, $p<0.05$) among second-generation than not-second-generation subjects (table 1). The analyses also revealed a significant decrease over time in the reported occurrence of intrusiveness ($F=8.76$, df=2, 180, $p<0.01$), hyperalertness ($F=11.53$, df=2, 180, $p<0.01$), and emotional numbing ($F=5.07$, df=2, 180, $p<0.05$).

DISCUSSION

Our results indicate that 1, 2, and 3 years after their participation in the 1982 Lebanon War, Israeli combat stress reaction casualties whose parents were Holocaust survivors had higher rates of PTSD and reported a larger average number of PTSD symptoms than their counterparts without such family history. The decrease in PTSD severity over time was steeper among not-second-generation than second-generation veterans. These findings point to retarded recovery from PTSD among children of Holocaust survivors.

Numerous factors may contribute to these differences. One is the heightened vulnerability of children of survivors to stress (6, 9). Although this study was based on a sample that was healthy before the war (i.e., they had all passed the physical and psychological tests for Israel Defense Forces recruitment as front-line soldiers), their exposure to combat seems to have unmasked a latent vulnerability that was not activated by less stressful life events.

The PTSD of the second generation may in effect be a reactivation of a latent posttraumatic syndrome deriving from their parents' Holocaust experience. An earlier study by our group (18, 19) showed that reactivated PTSD among soldiers who had had a combat stress reaction before the one in the Lebanon War was more intense and enduring than first time PTSD. We seem to be witnessing a similar phenomenon here, with the antecedent event not a previous combat stress reaction but the parents' Holocaust experience.

Another impediment to recovery may be related to the particular meaning that the combat stress reaction has for children of survivors. Almost every combat stress reaction casualty feels that he has failed, and most suffer agonies of shame and reduced self-esteem; however, among the second generation the sense of failure cuts deeper. Children of Holocaust survivors see themselves as guardians and protectors of their parents (4). In a very real sense, the second generation was raised to undo the damage that the Holocaust had brought to their parents' lives. The magnitude of this expectation probably intensifies both the stress on the battlefield and the failure implicit in a combat stress reaction.

Last, the survivor family itself may undermine recovery. As a result of their accentuated fear of loss, parents who are Holocaust survivors tend to have a greater difficulty than others with the real hardship of parting with their children (4). Recovery might be impeded by the excess of secondary gains to be had from the survivor parents' well-documented overprotectiveness (4). Also, survivor parents may have unconsciously discouraged the recovery of their children with combat stress reaction to avert the very real danger of their being sent back to the front and perhaps killed.

The clinical picture of the second generation is highly reminiscent of that of their survivor parents. Like their parents, they suffer from a relatively large amount of intrusive symptoms and hyperalertness. The PTSD in the second generation may involve an unmasking of Holocaust-related disturbances or reflect responses that the children "learned" from their survivor parents. For example, the second-generation PTSD casualty may have more war-related nightmares than his control group peers because he had seen and heard his parents venting their emotions.

The contribution of this study lies in its large sample size of subjects who were deemed physically and psychologically healthy before their participation in the 1982 Lebanon War and also in its prospective design. Nonetheless, numerous questions remain unanswered. We have no specific knowledge of the sociodemographic background and mental and physical status of our subjects' parents. We do not know whether they were in hiding, fought in the partisans, or were imprisoned in concentration camps; we know nothing about the magnitude of their losses, nor do we know which of the subjects' parents were actually in the Holocaust. As for the subjects, we have no knowledge of their birth order, their relationships with their parents, or their attitudes toward war, heroism, and aggression, nor do we fully understand the exact nature of the connection between the parents' Holocaust experience and their children's secondary traumatization. We suggest that future multivariate research, based on interviews rather than questionnaires, assess the specific nature of the Holocaust experience and identify the means by which the Holocaust trauma is transmitted from the survivors to their children.

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Drug-Induced Dystonia in Young and Elderly Patients

Gerard Addonizio, M.D., and George S. Alexopoulos, M.D.

This retrospective study examined the common notion that neuroleptic-induced dystonia is less frequent in elderly patients. The hospital records of 45 young patients and 45 elderly patients were reviewed. Thirty-one percent of the young patients developed dystonia, compared to 2% of the elderly patients. This significant difference did not appear to be the result of types of neuroleptics used, dose, or concomitant administration of anticholinergic drugs.

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Dystonia is a well-known side effect of neuroleptic drugs. It has been suggested that neuroleptic-induced dystonia is much more common in young patients (1–5). Unfortunately, there are several problems with these reports that have not been addressed. Often unaccounted for in making age-group comparisons are type of neuroleptic (2, 5), dose (5), and concomitant use of anticholinergic drugs (1, 5). Another problem has been that doses of various neuroleptics have been treated only as chlorpromazine equivalents (2), which may be only a general estimate of a neuroleptic's ability to cause extrapyramidal symptoms. In addition, reported results are often based on dichotomized age groups, with a relatively early age cutoff (1, 4) and few patients above the age of 60 included (2). One textbook of geriatric psychopharmacology states that dystonic reactions "seem to be less common in older patients, although careful comparative studies of incidence have not been conducted" (6).

In this study we assessed the prevalence of dystonia in a group of young and elderly patients and examined the contribution of type of neuroleptic and dose to this effect. Other variables that might account for differences in prevalence were also explored.

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METHOD

We examined the hospital records of 45 patients between the ages of 18 and 35 years (mean age=26) and 45 patients between the ages of 60 and 80 (mean age=69); these patients had been consecutively admitted to acute inpatient units at New York Hospital, Westchester Division. Subjects were chosen who met *DSM-III* criteria for diagnoses of schizophrenia, schizophreniform disorder, schizoaffective disorder, paranoia, and acute paranoid disorder. Patients with affective disorders were excluded because elderly patients with these diagnoses are usually treated with much lower doses of neuroleptics than are young patients, thereby making it impossible to do group comparisons on similar doses of neuroleptics. Patients were selected who had been treated with haloperidol, fluphenazine, trifluoperazine, or thiothixene. For patients included in the study, the maximum dose of haloperidol and fluphenazine was 20 mg/day and the maximum dose of trifluoperazine and thiothixene was 50 mg/day. Ceiling doses were chosen to ensure similar treatment dosage for the two groups. Subjects were excluded if they had organic brain disease, treatment with depot neuroleptics, neuroleptic treatment within 1 week before admission, or a history of a movement disorder not associated with neuroleptics. Because dystonia occurs soon after neuroleptic treatment is started, only the first 15 consecutive days after the initiation of neuroleptic treatment were considered. Data were collected on the type and dose of neuroleptic and evidence of dystonic reactions. Additional data included use of anticholinergics, other antiparkinsonian medication, antidepressants, lithium, and benzodiazepines, all of which may affect the development of dystonia.

Data were analyzed by using chi-square analysis with Yates' correction, Student's t test, and logistic regression. All levels of significance are two-tailed.

RESULTS

Thirty-one percent of the young patients receiving neuroleptics developed dystonia, while only 2% of the elderly patients developed a similar reaction. This difference was statistically significant ($\chi^2=11.52$, $df=1$, $p<0.001$). Table 1 presents data on the relationship between age group and development of dystonia in patients receiving the same neuroleptic. Young pa-

TABLE 1. Neuroleptic Use in Young and Elderly Patients With or Without Dystonia

Group	Sex		Chlorpromazine Equivalents			Haloperidol			Thiothixene			Fluphenazine			Patients Taking Anticholinergics
				Dose (mg/day)			Dose (mg/day)			Dose (mg/day)			Dose (mg/day)		
	M	F	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Dystonia															
Young	7	7	14	385.7	157.4	7	7.4	2.5	3	13.3	2.9	4	10.0	4.1	0
Elderly	0	1	1	700.0		1	14.0		0			0			0
No dystonia															
Young	10	21	31	705.7	251.0	7	13.4	6.0	18	33.3	11.3	6	17.3	4.8	8
Elderly	5	39	44[a]	408.5	262.1	25	8.6	6.1	8	13.8	5.7	6	10.5	5.1	2

[a]Includes five patients treated with trifluoperazine.

tients receiving haloperidol developed dystonia more frequently than older patients receiving this drug ($\chi^2=9.40$, df=1, $p<0.01$). There was a trend in the same direction for patients receiving fluphenazine ($\chi^2=1.42$, df=1, $p<0.30$). The small number of patients who developed dystonia while receiving thiothixene (table 1) did not permit statistical comparison of dystonia between old and young subjects. Since there were no young patients treated with trifluoperazine, no group comparisons could be done.

The dose of each neuroleptic and chlorpromazine equivalents were compared among young and old patients with and without dystonia (table 1). Data analysis also included chlorpromazine equivalents of neuroleptics so that whole-group comparisons could be done despite treatment with different neuroleptics. The chlorpromazine equivalents dose of young patients who developed dystonia was much lower than that of young patients who did not develop dystonia ($t=4.38$, df=43, $p<0.001$); this finding suggests that certain patients are susceptible to this reaction. In comparing chlorpromazine equivalents of young dystonic patients and elderly nondystonic patients, we found no significant difference in dose ($t=0.31$, df=56, n.s.). Logistic regression was employed using the whole sample (N=90) in order to examine the effects of age, use of anticholinergic drugs, and dose of neuroleptics expressed as chlorpromazine equivalents. A forced last entry model showed a significant overall effect of the three variables on development of dystonia ($\chi^2=32.26$, df=3, $p<0.00001$). When each of the three variables was examined separately, young age appeared to have the strongest association with the development of dystonia ($\chi^2=13.72$, df=1, $p<0.001$). There was a significant negative association between dose of neuroleptic expressed as chlorpromazine equivalents and development of dystonia ($\chi^2=6.83$, df=1, $p<0.009$). There was no significant effect of anticholinergics on development of dystonia ($\chi^2=0.12$, df=1, $p<0.72$).

Young dystonic patients and elderly nondystonic patients received comparable doses of haloperidol ($t=0.48$, df=31, n.s.), fluphenazine ($t=0.16$, df=8, n.s.), and thiothixene ($t=0.01$, df=9, n.s.). Eight young patients but only two elderly patients who did not develop dystonia started a regimen of anticholinergic medication (table 1). Therefore, the rarity of dystonia in elderly patients could not be explained by use of anticholinergics. Use of benzodiazepines, lithium, antidepressants, and other antiparkinsonian agents was very rare in both groups of patients. In the young group, two were treated with benzodiazepines, four with lithium, one with antidepressants, and none with other antiparkinsonians. In the elderly group, three were treated with benzodiazepines, three with lithium, two with antidepressants, and none with other antiparkinsonians.

DISCUSSION

This study confirms the clinical impression that neuroleptic-induced dystonia is more common in young patients (6) and also indicates that dystonia is relatively rare in the elderly. In addition, it appears that this finding is not a result of differences in the type of neuroleptic, dosage, or concomitant use of anticholinergic drugs. Because diagnoses in this population were confined to schizophrenia and paranoid disorders, our conclusions may not be generalizable to patients with other diagnoses. In addition, the significantly higher frequency of dystonia in young patients may have been affected by the greater number of men in the young population. In one survey, acute dystonia was twice as frequent in men (5). However, it is unlikely that this difference could have fully accounted for the dramatic difference in dystonia in the two groups. Our results are limited by the constraints of a retrospective study and dictate the need for further prospective investigation.

These results have important clinical implications for the treatment of elderly patients. The anticholinergic effects of medication often have a devastating effect in the elderly. Common complications include confusion, urinary retention, attacks of narrow angle glaucoma, and severe constipation sometimes leading to the development of an ileus (6). The prevention of acute dystonia may be the only justification for prophylactically starting anticholinergic drugs with neuroleptics; however, our data suggest that the low risk

of developing dystonia does not justify this treatment strategy with elderly patients.

Why neuroleptic-induced dystonia occurs less frequently with aging remains unclear. Cumulative exposure to neuroleptics over many years may in some way immunize against the development of acute dystonia, although some of our elderly patients had had much less prior neuroleptic treatment than many young patients. Chart documentation of this information was not adequate enough to come to meaningful conclusions. Evidence from human and animal studies suggests that acute dystonic reactions are related to enhanced striatal dopamine activity and dopamine release provoked by acute administration of neuroleptic drugs (7). Age-related degeneration of the striatum may sufficiently diminish this acute enhancement of dopaminergic activity and therefore decrease the likelihood of dystonia. Until the pathophysiology of dystonia becomes better understood, this explanation can only be considered speculative. In future studies of dystonia, researchers should remain mindful of potential age-related factors.

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Who Seeks Mental Health Care in China? Diagnoses of Chinese Outpatients According to *DSM-III* Criteria and the Chinese Classification System

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The authors gave DSM-III *diagnoses to 116 Chinese psychiatric outpatients in Shanghai and compared them with the diagnoses of the same patients made by a Chinese psychiatrist according to Chinese criteria. Affective disorders were the most common* DSM-III *diagnoses, accounting for 26.7% of the sample. A full range of psychopathology, including schizophrenia, organic mental disorders, adjustment disorders, anxiety disorders, and paranoid disorders, was seen. Some consistent differences in diagnosis by Chinese and Western standards, especially in the area of major depression, were found. The authors discuss the implications for interpreting psychiatric studies from China and for future cross-cultural research comparing U.S. and Chinese diagnoses.*

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As interest in the contributions of genetic, environmental, and cultural factors to major psychiatric disorders continues, transcultural psychiatry assumes increasing importance. China, with its population of 1.6 billion and a tiered, centralized health care system, offers a rich potential for comparative studies. For cross-cultural research to be valid, a common vocabulary and perception of disease must exist among those assigning diagnoses and carrying out such studies. In 1984 the People's Republic of China adopted its first psychiatric diagnostic manual (1), and most psychiatric institutions in China are now attempting to diagnose patients in accordance with its criteria. This makes it possible to compare diagnoses by two different classification systems (*DSM-III* and the Chinese psychiatric manual). Thus, the present study was undertaken to establish preliminary groundwork for comparative studies. Using an outpatient population in China, we investigated two questions: 1) What are the *DSM-III* diagnoses for new patients seeking outpatient mental health care in China? 2) How do the *DSM-III* diagnoses assigned to these patients compare with their Chinese psychiatric diagnoses?

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METHOD

Our study sample consisted of all new outpatients who came to the Shanghai Mental Health Center for an evaluation in December 1986 and January 1987. The Shanghai Mental Health Center serves a catchment area of more than 11 million people, and the staff sees more than 400 patients a day (2). Of these 400, only two to 10 patients each day are new. During the study, 134 new patients came to the outpatient clinic for evaluation.

Each patient was initially seen by one of the attending Chinese psychiatrists at the outpatient clinic. The psychiatrist wrote down the patient's history and the results of a mental status examination and made a psychiatric diagnosis in accordance with the Chinese Classification of Mental Disorders (1). Next, the patient was seen by a Western psychiatrist (L.L.A.) who was blind to the initial diagnosis. The patient was interviewed with the aid of one of several interpreters (Q.H., H.Q., W.W., X.M.), all of whom were psychiatrists at the Shanghai Mental Health Center and spoke fluent English. The patient's history, as recorded by the initial psychiatrist, was first translated to the Western psychiatrist by the interpreter, reading directly from the written record. When the patient was available, a semistructured interview ensued; the *Quick Reference to Diagnostic Criteria From DSM-III* was used during the interview to confirm information in the history and to obtain additional information. When the patient could not be seen, the written record was reviewed and the patient was included in the study only if sufficient information for making a *DSM-III* diagnosis had been given. To ensure that a *DSM-III* diagnosis was not based on incorrectly translated

material or misinterpreted information, the Western physician also assigned to each patient a diagnosis in accordance with the Chinese classification system. In this way, the validity of the information received could be determined by comparing the number of times the Chinese psychiatrist's diagnosis and the Western psychiatrist's "Chinese diagnosis" were in agreement. The Western psychiatrist was familiar with the use of the Chinese classification manual, since she had spent 1 month on the inpatient wards before the study began.

Of the 134 consecutive new patients at the clinic, 116 (58 men and 58 women) were included in the study. For the men, the mean±SD age was 34±15; for the women, it was 37±20 years. One hundred two of the patients were interviewed; 14 were not interviewed, but their recorded histories were complete enough to assign a *DSM-III* diagnosis. The remaining 18 of the 134 patients were not seen and were not included in the study because insufficient documentation of symptoms in the recorded histories precluded assigning a diagnosis.

RESULTS

Of the 116 Chinese diagnoses assigned by the Western physician, 104 (89.7%) were in agreement with the diagnoses given by the Chinese psychiatrist, affirming a high rate of accurately translated and interpreted information. *DSM-III* diagnoses could be made easily for all but five of the 116 Chinese psychiatric outpatients. The range of psychopathology is demonstrated in table 1. Among the patients with a diagnosis of atypical psychosis or an anxiety disorder, a predominance of women was found. In no other diagnostic category was there a substantial difference between the sexes.

In the majority of cases (87 of 116, or 75.0%), the diagnosis given by the Chinese psychiatrist was in accordance with the *DSM-III* diagnosis assigned by the Western psychiatrist. This was particularly true in the schizophrenic disorders category. It should be noted that the Chinese classification gives a definition of schizophreniform disorders which is similar to that in *DSM-III*, but the duration of symptoms may be less than 3 months. If symptoms persist for more than 3 months, then a diagnosis of schizophrenia is made. With this difference taken into consideration, there was no instance in which a *DSM-III* diagnosis of a schizophrenic disorder differed from the Chinese diagnosis.

There were certain categories, however, in which diagnoses frequently differed (see table 2). Ten of the 31 patients (32.2%) diagnosed as having an affective disorder according to *DSM-III* criteria were not diagnosed as such by the Chinese psychiatrist; i.e., the diagnoses fell into different categories, including schizophrenic disorders, anxiety disorders, neurasthenia, and paranoid state. Of the 21 patients who were given a diagnosis of major depression according to *DSM-III*, only slightly more than half (N=12, or 57.1%) were given a similar diagnosis by the Chinese psychiatrists. Of the seven manic patients, six (85.7%) were given a similar Chinese diagnosis. It should be noted that four of the patients who were diagnosed as depressed or manic by *DSM-III* standards exhibited hallucinations or delusions, and all four of them were diagnosed as schizophrenic by the Chinese psychiatrists. Patients in whom depression was accompanied by multiple somatic complaints often received Chinese diagnoses of anxiety or neurasthenia.

Adjustment disorder is a diagnosis that does not

TABLE 1. *DSM-III* Diagnoses of 116 Shanghai Psychiatric Hospital Patients

Diagnosis	Number of Patients		Total	
	Male	Female	N	%
Affective disorders	15	16	31	26.7
Major depression	9	11	20	17.2
Bipolar disorder	5	4	9	7.8
Manic	4	3	7	6.0
Depressed	0	1	1	0.9
Mixed	1	0	1	0.9
Cyclothymic disorder	1	0	1	0.9
Dysthymic disorder	0	1	1	0.9
Schizophrenic disorders	11	14	25	21.5
Organic mental disorders	7	6	13	11.2
Dementia	3	4	7	6.0
Delirium	2	0	2	1.7
Organic affective syndrome	1	1	2	1.7
Organic personality syndrome	1	0	1	0.9
Organic hallucinosis (visual)	0	1	1	0.9
Adjustment disorder[a]	6	4	10	8.6
Anxiety disorders	1	5	6	5.2
Panic disorder	0	1	1	0.9
Phobic disorder	1	0	1	0.9
Obsessive-compulsive disorder	0	2	2	1.7
Generalized anxiety disorder	0	2	2	1.7
Other	4	2	6	5.2
Sleep disorders	2	1	3	2.6
Life circumstance problem	1	1	2	1.7
Epilepsy without psychiatric complication	1	0	1	0.9
Paranoid disorders	3	2	5	4.3
Atypical psychosis[b]	0	5	5	4.3
Undiagnosed	4	1	5	4.3
Brief reactive psychosis	1	1	2	1.7
Alcohol/drug dependence	2	0	2	1.7
Eating disorder	0	1	1	0.9
Schizoaffective disorder	0	1	1	0.9
Mental retardation	1	0	1	0.9
Conversion disorder	1	0	1	0.9
Depersonalization disorder	0	1	1	0.9
Mixed personality disorder	1	0	1	0.9

[a]Dissatisfaction with one's job and difficulty in a love relationship were the two most common causes of distress.
[b]Of these five patients, three had a single paranoid delusion, the short duration of which precluded a diagnosis of a paranoid disorder.

TABLE 2. Differences Between *DSM-III* and Chinese Diagnoses of Shanghai Psychiatric Hospital Patients

DSM-III Diagnosis	Chinese Diagnosis
Major depression (N=9)	Schizophrenia (N=3)
	Anxiety disorder (N=3)
	Neurasthenia (N=2)
	Psychogenic paranoia (N=1)
Bipolar disorder, manic (N=1)	Schizophrenia (N=1)
Adjustment disorder (N=10)	Psychogenic depression (N=3)
	Depressive neurosis (N=3)
	Obsessive neurosis (N=2)
	Anxiety neurosis (N=1)
	Psychogenic paranoid state (N=1)
Organic mental disorder (N=1)	Hebephrenic schizophrenia (N=1)
Bulimina (N=1)	Unknown (N=1)
Obsessive-compulsive disorder (N=1)	Neurasthenia (N=1)
Atypical psychosis (N=3)	Paranoid state (N=2)
	Paranoid schizophrenia (N=1)
Mixed personality disorder (N=1)	Obsessive neurosis (N=1)
Diagnosis deferred (N=2)	Phobic neurosis (N=1)
	Neurasthenia (N=1)

exist in the Chinese classification system. Thus, all 10 patients who had a *DSM-III* diagnosis of adjustment disorder received a different Chinese diagnosis (see table 2). There were nine other differences in diagnosis (also shown in table 2). Two patients for whom *DSM-III* diagnoses were deferred received diagnoses (neurasthenia and phobic neurosis) by the Chinese psychiatrists.

In all, there were 29 cases (25.0%) in which the *DSM-III* diagnosis differed from the Chinese classification diagnosis assigned by the Chinese psychiatrist.

Seventeen of the 116 patients (nine female and eight male) were admitted to the hospital. Of the 21 depressed patients, only three (14.3%) were admitted, while four (57.1%) of the seven manic patients were hospitalized. The other admissions to the hospital included four patients with schizophreniform disorder, two with organic mental disorders, one with schizophrenia, one with brief reactive psychosis, one with mental retardation, and one with depersonalization disorder. The rest of the patients were scheduled for follow-up appointments as outpatients.

DISCUSSION

Our study demonstrated a wide range of psychopathology in a sample of Chinese outpatients, as well as the applicability of *DSM-III* criteria to this sample. For the vast majority of the patients (111 of 116, or 95.7%), a *DSM-III* diagnosis could be made without difficulty.

When we compared the Chinese psychiatric diagnoses with those assigned by using *DSM-III*, most (75.0%) of the diagnoses were in agreement. The confirmation of these similarities is of fundamental importance, because it assures that Chinese and Western physicians perceive and define disease similarly, lending credibility and reliability to cross-cultural prevalence studies. Perhaps such a high degree of overlap should not be surprising, since the Chinese diagnostic manual is based in part on *DSM-III*.

There were, however, some important differences, most notably in the diagnosis of depression. Almost half of the patients given a *DSM-III* diagnosis of major depression were not given such a diagnosis by the Chinese classification standards. Indeed, all depressed patients with delusions or hallucinations were diagnosed as schizophrenic by the Chinese psychiatrists, probably because of the strong influence of Bleuler on psychiatry in China (3). Although during the late 1950s (before the Cultural Revolution), academic psychiatry in China was largely under the influence of the Soviet schools, diagnosis of mental disorders before that time had been deeply influenced by German and Western European psychiatric thought (4). In a retrospective study of inpatients, Xu and Xia (5) found that of 489 patients with affective disorder, 42 (8.6%) had been misdiagnosed as schizophrenic; half of these 42 patients had a predominantly psychotic or delusional depression, and the other half had predominantly "negative symptoms" (decreased affective responsivity) or depersonalization experiences, which were viewed as "characteristically schizophrenic."

We also observed that if a depressed patient's symptoms were predominantly somatic, the patient was, more often than not, given a diagnosis of anxiety disorder or neurasthenia. It has been noted previously that depressed Chinese patients tend to manifest more somatic symptoms and may therefore be given diagnoses of somatic or neurotic disorders rather than major depression (6–8). Our study supports this; although many of the patients were able to verbalize feelings of sadness, hopelessness, helplessness, tearfulness, and guilt, those who concomitantly verbalized somatic complaints were often assigned an anxiety rather than an affective diagnosis in the Chinese classification system. These differences between the Eastern and Western uses of the diagnoses of anxiety, depression, and schizophrenia may reflect critical differences between Chinese and Western definitions and/or perceptions of specific psychiatric entities. It is important to consider such differences when interpreting prevalence studies from both cultures. These differences could account for the discrepant rates of depression—up to 20% in the United States and 0.08% in China (9)—reported in the two countries. When *DSM-III* criteria are applied to a Chinese psychiatric population, depression seems common.

In one of the seven patients who presented with a *DSM-III* diagnosis of bipolar disorder, manic, the Chinese diagnosis differed: the one manic patient with mood-congruent auditory hallucinations was diagnosed by the Chinese as schizophrenic despite demonstrated hypersomnia, hypersexuality, insomnia, pressured speech, and grandiose ideation. While four

(57.1%) of the seven manic patients were admitted to the hospital, only three (14.3%) of the depressed patients were admitted. Several reasons for this are possible. The hospital admission criterion at Shanghai Mental Health Center is psychosis, and the majority of the depressed patients were not psychotic. Furthermore, while suicidal ideation was passive if it was present at all, only one of the depressed patients had attempted suicide, and this was secondary to command hallucinations. Thus, it appears that a nonsuicidal, withdrawn person is well tolerated by family and society in the Chinese culture. Conversely, mania is not well tolerated by a community that greatly values conformity and obedience in its members. The intolerance of manic behavior compared to depressed behavior was reflected in the higher admission rate for manic patients, two of whom were hypomanic by Western standards.

Yan Shan-Ming et al. (10) noted that of 268 consecutive patients admitted to a Chinese hospital, 47 (17.5%) were manic and only 13 (4.9%) were depressed, according to *DSM-III* criteria. While that study supported the notion that more manic patients than depressed patients may be hospitalized, those observations also point to the great need for outpatient studies; inpatient samples may inaccurately reflect the prevalence of psychiatric disorders in the total psychiatric population. (This may also be true in the United States, where hypomanic behavior is perhaps better tolerated by the society than depression with suicidal ideation, and thus, in contrast to China, patients with bipolar II disorder may be more likely to be hospitalized when depressed than when hypomanic.) By looking only at inpatient samples, one could draw the incorrect conclusion that depression is rare in China. Inpatient diagnoses may tell us more about the cultural determinants of hospitalization than about the true prevalence of psychiatric disorders in a given population.

The high rates of organic mental disorder seen in our outpatient study may reflect the high prevalence reported in China as a whole. Dementia (including the senile and cerebrovascular-related types) was the most common kind of organic mental disorder, which is consistent with the results of Chinese field studies (11, 12).

Several issues remain and require further investigation. Patients with paranoid disorders and paranoia-related syndromes were observed frequently at the outpatient clinic. Is there a higher prevalence of paranoid disorders in China than in the United States? Given China's history, could this be culturally determined? In addition, our study showed no difference between the sexes in the prevalence of depression in China, whereas in the United States, women predominate among depressed patients.

Outpatient admission studies done in the United States in 1975, which used *DSM-II* criteria, showed high rates of depressive disorders (12.9%), situational disorders (14.2%), and schizophrenia (10.5%) (13), as we saw in Chinese outpatients in this study. The results of U.S. outpatient studies in 1985, in which *DSM-III* criteria were used, will be published this year. Those results can be compared in the future with the results of outpatient studies in China that use *DSM-III* criteria.

To our knowledge, no other outpatient studies using *DSM-III* have been done to date in China. Because inpatient studies reveal a limited scope of psychopathology, generalizing about the psychiatric population at large from inpatient studies is misleading. Perhaps only by studying Chinese psychiatric outpatients can the full range of psychiatric disorders be viewed and compared with those in the United States and elsewhere. This preliminary study revealed many areas of overlap, but also several areas of differences, between the Chinese and Western diagnostic criteria and perceptions of disease. It also demonstrated the use of *DSM-III* axis I diagnoses as a tool in making cross-cultural comparisons of psychiatric disorders. We hope that the results presented here will aid in future interpretations of U.S. and Chinese prevalence studies and will help further the development of a common psychiatric vocabulary for use in cross-cultural research.

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Lack of Association Between HLA Antigens and Anorexia Nervosa

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Studies of the human leukocyte antigen (HLA) system were performed in 37 patients with anorexia nervosa to confirm an alleged association with HLA-B16 and haplotype HLA-A26,B38. No correlation between anorexia nervosa and HLA, including HLA-DR, could be found.

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Anorexia nervosa is a disease characterized by extreme weight loss, body image disturbances, and intense fear of becoming obese. Family studies have shown a relatively frequent occurrence of affective disorders in relatives of patients with anorexia nervosa (1). A high concordance of anorexia nervosa in monozygotic twins and a low concordance in dizygotic twins have been observed (2). Thus, family and twin studies suggest a genetic predisposition for affective disorders and anorexia nervosa, respectively. One method of demonstrating such a genetic factor is to show an association between a disease and the human leukocyte antigen (HLA) system. Associations between the HLA system and affective disorders have been shown by Shapiro et al. (3), who found a high frequency of HLA-B16 in bipolar affective disorder, and by Weitkamp et al. (4), who studied HLA haplotype sharing in families with depressive disorders. However, these findings have been challenged by studies that did not confirm such an association (5–7). To our knowledge, only one study of HLA and anorexia nervosa has been published to date, and it showed a high frequency of the antigen HLA-B16 (B38+B39) and the haplotype HLA-A26,B38 (8). The current study was undertaken to verify these findings, as they have been interpreted as preliminary. Furthermore, we extend the data on HLA and anorexia nervosa by the investigation of HLA-DR antigens.

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METHOD

We included in the study 37 Caucasian women who met the *DSM-III* criteria for anorexia nervosa. The patients, all young adults between 16 and 32 years of age (mean±SD=22.5±4.8 years), were hospitalized for treatment of the disease. All patients were typed for 15 HLA-A, 35 HLA-B, eight HLA-C, and 10 HLA-DR antigens according to standardized methods (9). Informed consent was obtained from all patients.

The control group consisted of 450 individuals typed for HLA-A, -B, and -C; they represented both sexes, lived in the same area as the patients, ranged in age from 19 to 56 years, and were free of any known medical or psychiatric disorders. The last 120 of the 450 control subjects were also typed for HLA-DR antigens; the HLA-DR typing technique was established several years later than the HLA-A, -B, and -C typing method. The control subjects typed for HLA-DR therefore were selected by chance, so a bias in the control subjects can be excluded.

We employed 2×2 comparisons to compare the frequency of each of the HLA antigens tested in the patients with that frequency in the healthy control subjects. For statistical evaluation, the chi-square test with Yates' correction for small sample sizes was used. According to Svejgaard et al. (10), the p value resulting

TABLE 1. Frequencies of HLA Antigens in Patients With Anorexia Nervosa and in Healthy Control Subjects

Antigen or Haplotype	Anorexia Nervosa Patients			Healthy Control Subjects			χ^2 (df=1)
		With Antigen			With Antigen		
	N	N	%	N	N	%	
HLA-A or -B antigen	37			450			
HLA-A26		2	5.4		37	8.2	0.085
HLA-B16 (B38+B39)		2	5.4		40	8.8	0.177
HLA-B38		1	2.7		22	4.8	0.039
HLA-B39		1	2.7		18	4.0	0.024
HLA-A26,B38 haplotype	37	1	2.7	450	9	2.0	0.098
HLA-DR antigen	37			120			
HLA-DR1		5	13.5		31	25.8	2.647
HLA-DR2		7	18.9		40	33.8	2.801
HLA-DR3		6	16.2		21	17.5	0.035
HLA-DR4		9	24.3		21	17.5	0.852
HLA-DR5		9	24.3		37	30.8	0.578
HLA-DRw6		12	32.4		19	15.8	4.489[a]
HLA-DR7		10	27.0		30	25.8	0.061
HLA-DRw8		2	5.4		9	7.5	0.462
HLA-DRw9		1	2.7		1	0.8	0.002
HLA-DRw10		1	2.7		0	0.0	0.390

[a] $p<0.05$; $p>0.05$ when corrected for the number of antigens tested according to the method of Svejgaard et al. (10).

from each comparison was corrected with the number of comparisons performed.

RESULTS

As shown in table 1, there was no significant difference in the frequency of any HLA-A, -B, -C, or -DR antigen between the patients with anorexia nervosa and the healthy control subjects. The significantly higher frequency of HLA-DRw6 in the patients vanishes when appropriate statistical corrections are performed.

DISCUSSION

A high frequency of HLA-B16 (B38+B39) in anorexia nervosa and an association of this disorder with the haplotype HLA-A26,B38 have been suggested by the work of Biederman et al. (8). The findings of the present study do not support such an association. An additional testing of HLA-DR antigens also did not show any association of these antigens with anorexia nervosa.

Differences in the ethnic backgrounds of the samples studied by Biederman et al. and by us cannot explain the contradictory results, since the samples in both studies consisted exclusively of non-Jewish Caucasians. The different results could be due to heterogeneity of the disorder, although the same diagnostic criteria for anorexia nervosa were used in both studies.

Originally, the finding of a high frequency of HLA-B16 in patients with anorexia nervosa and in patients with affective disorders suggested that the two disorders might share a common genetic vulnerability (8). This view was supported by the finding that a subgroup of patients with anorexia nervosa also develops nonbipolar major depressive disorders (1). Other studies (5, 6) could not confirm an association of HLA antigens with affective disorders. Also, Biederman et al. (7), who described the association of HLA with anorexia nervosa, could not find an association between either HLA-B16 or the haplotype HLA-A26,B38 and either bipolar or nonbipolar depression.

The lack of association between HLA antigens and anorexia nervosa in the present study does not exclude a genetic predisposition for this disorder, as twin studies showed a high concordance for anorexia nervosa in monozygotic pairs (2). Our findings only suggest that the determinants of susceptibility are not associated with the HLA system. If a genetic predisposition for anorexia nervosa exists, genetic factors other than HLA antigens have to be involved.

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Exacerbation of Psychosis After Discontinuation of Carbamazepine Treatment

C.W. Chris Heh, M.D., John Sramek, Pharm.D., John Herrera, Ph.D., and Jerome Costa, M.D.

Carbamazepine alone or carbamazepine plus neuroleptic was administered to 20 chronic schizophrenic patients. Upon abrupt discontinuation two of the 20 patients had exacerbations of their psychoses characterized by paranoia, hostility, and agitation. The authors discuss the possibility of a carbamazepine withdrawal syndrome.

(Am J Psychiatry 1988; 145:878–879)

Carbamazepine is widely used in various psychiatric disorders. It is clinically efficacious for the treatment of acute mania and the long-term prophylaxis of bipolar affective illness (1). It has been reported to be effective for the treatment of patients with schizoaffective and schizophreniform disorders (2) and excited psychotic states, including violent and aggressive schizophrenic patients (3). Although carbamazepine's clinical efficacy for the treatment of chronic schizophrenia is still being investigated, we report an exacerbation of psychosis and possible carbamazepine withdrawal syndrome in two chronic schizophrenic patients with negative symptoms after the abrupt discontinuation of carbamazepine treatment. The two patients reported here were part of a larger study in which 20 chronic schizophrenic patients received either carbamazepine alone or carbamazepine plus neuroleptic. Both patients had EEGs before the carbamazepine trial, and they showed no evidence of a seizure disorder.

CASE REPORTS

Case 1. Mr. A, a 37-year-old white chronic schizophrenic inpatient, had been maintained on a regimen of oral chlorpromazine, 250 mg q.i.d., for several years. His usual mental status primarily consisted of negative symptoms—apathy, affective blunting, anhedonia, and asociality. He spent the majority of his time sitting quietly in a chair, withdrawn and not interactive with peers or staff, and occasionally whispering and mumbling to himself. Mr. A's chlorpromazine regimen was abruptly discontinued, and he was treated with carbamazepine in an attempt to ameliorate his negative symptoms. He was initially given 200 mg b.i.d. orally, and the dose was titrated quickly to 200 mg q.i.d.; the therapeutic serum level was 11 μg/ml (normal, 8–12 μg/ml). During the 6-week trial of carbamazepine, weekly ratings with the Brief Psychiatric Rating Scale (BPRS) essentially showed no change in his total score between baseline and endpoint.

At the end of the trial, carbamazepine was abruptly discontinued, and oral chlorpromazine was reinstated at the prior dose of 250 mg q.i.d. Three days after chlorpromazine was reinstated, Mr. A began to show overt positive signs of psychosis. He would no longer sit quietly in his chair; rather, he would often get up, go to the telephone, and scream obscenities into the receiver. In spite of increasing doses of chlorpromazine, he became acutely paranoid and hostile, claiming that "you doctors are messing with my mind." He began refusing all oral medications and eventually required seclusion for administration of even higher doses of intramuscular chlorpromazine. There was no clinical evidence of akathisia or parkinsonian symptoms. Ten days after the discontinuation of carbamazepine, Mr. A returned to his baseline mental status with a maintenance chlorpromazine dose of 400 mg q.i.d.

Case 2. Mr. B, a 48-year-old Hispanic chronic schizophrenic inpatient, had been maintained on a regimen of oral haloperidol, 5 mg t.i.d., and benztropine, 2 mg b.i.d., for the past 6 months. His baseline haloperidol serum level was 7 ng/ml. As with Mr. A, Mr. B's mental status was predominantly composed of negative symptoms—alogia, apathy, avolition, and severe affective blunting. Mr. B spent the majority of his time on the hospital grounds, frequently drinking copious amounts of fluids, pestering fellow patients for cigarettes, and sitting on the bench giggling to himself.

Oral carbamazepine was added adjunctively to Mr. B's haloperidol regimen at an initial dose of 200 mg b.i.d. The dose was titrated to 200 mg t.i.d., which resulted in a therapeutic blood level of 9 μg/ml. After 5 weeks of carbamazepine treatment, it was evident that there was no appreciable change in Mr. B's clinical state or BPRS scores. Carbamazepine treatment was abruptly discontinued, and 2 days later Mr. B began to show increasing signs of agitation, paranoia, hostility, and aggressive behavior. A staff member observed him striking a female patient, claiming, "She was trying to take one of my testicles." Mr. A's haloperidol serum level was 8 ng/ml. The dose of haloperidol was titrated to 10 mg q.i.d., but Mr. B still became increasingly volatile and belligerent. He struck a staff member, for which his

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grounds pass was revoked, and he eventually required seclusion and restraints. There was no clinical evidence of akathisia or parkinsonian symptoms. Seven days after carbamazepine discontinuation, Mr. B returned to his baseline mental status with a higher maintenance dose of haloperidol (15 mg q.i.d.) and a benztropine dose of 2 mg b.i.d.

DISCUSSION

Both case reports show a striking exacerbation of psychosis occurring after the abrupt discontinuation of carbamazepine treatment. This exacerbation was characterized predominantly by positive symptoms—paranoia, agitation, delusions, and hostility. It is important to note that before the discontinuation of carbamazepine treatment, both patients had shown no overt positive psychotic symptoms for at least 6 months. Both patients dramatically required seclusion for their hostile and aggressive behavior. Mr. B required restraints, which had never been needed in the 2 years before this most recent episode. Furthermore, both patients required increasing doses of neuroleptics to ameliorate their psychotic exacerbations.

Interestingly, carbamazepine is widely used in Europe for the treatment of alcohol withdrawal (4) and recently has been reported to be effective for alprazolam withdrawal (5). Although carbamazepine's mechanism of action for the alleviation of withdrawal symptoms is still unknown, one may ask if carbamazepine itself may be associated with a withdrawal syndrome. It is well known that carbamazepine and neuroleptics are not addictive in the pharmacological sense, as are alcohol and benzodiazepines. However, low-potency neuroleptics, especially chlorpromazine and thioridazine, are associated with a neuroleptic withdrawal syndrome, which can appear as a worsening of psychosis (6). Hence, the worsening of psychosis after the abrupt withdrawal of carbamazepine is plausible. In fact, a recently published study (7) showed a "clear deterioration after discontinuation of carbamazepine" in 11 acutely psychotic schizophrenic or schizoaffective patients. These patients were treated with carbamazepine plus haloperidol, and after 28 days carbamazepine was abruptly discontinued while haloperidol administration was maintained. The two case reports presented here indicate that this exacerbation of psychosis can occur in chronic schizophrenic patients as well as those with acute episodes.

Although the mechanism(s) of action responsible for the exacerbation of psychosis after abrupt discontinuation of carbamazepine are unknown, the following are appealing hypotheses. Carbamazepine has been reported (8, 9) to decrease probenecid-induced CSF accumulations of homovanillic acid (HVA), which indicates that carbamazepine decreases overall dopaminergic turnover. Hence, we can postulate that with the abrupt discontinuation of carbamazepine a rebound phenomenon occurs that is characterized by an increase in dopamine turnover through, perhaps, a disinhibition of presynaptic firing. This, of course, can lead to a hyperdopaminergic state and an exacerbation of psychosis, which would require greater neuroleptic blockade to restore the system to its former level.

Another hypothesis, similar to the dopaminergic hypothesis, is the noradrenergic rebound that has been reported after the abrupt discontinuation of tricyclic antidepressant treatment. Tricyclics (10) and carbamazepine (9) have both been shown to decrease norepinephrine turnover. Upon abrupt discontinuation of tricyclic treatment, a rebound phenomenon can occur that is characterized by an increase in norepinephrine firing and turnover and the clinical manifestations of anxiety, agitation, and even manic symptoms (10). A similar noradrenergic mechanism for the exacerbation of psychosis after discontinuation of carbamazepine is plausible given that carbamazepine has antidepressant properties (8) and has a chemical structure similar to that of tricyclic antidepressants.

Clinicians should be aware of the possibility of worsening psychosis with the abrupt withdrawal of carbamazepine. It is already well known that the abrupt withdrawal of classical neuroleptics can lead to a withdrawal syndrome. Carbamazepine is a CNS depressant and has pronounced CNS activity; therefore, a withdrawal syndrome is plausible, especially considering the effects of carbamazepine on the dopaminergic and noradrenergic systems. However, further reports and controlled studies will be needed to further clarify the existence, frequency, and mechanism(s) of action of a carbamazepine withdrawal syndrome.

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ECT-Induced Postictal Delirium and Electrode Placement

Ismael Leechuy, M.D., Richard Abrams, M.D., and Joanne Kohlhaas

The authors report eight instances of ECT-induced postictal (emergence) delirium that occurred after bilateral ECT, right unilateral ECT, or left unilateral ECT. They conclude that postictal delirium is a random phenomenon unrelated to lateralized hemispheric mechanisms.

(Am J Psychiatry 1988; 145:880–881)

ECT-induced postictal (emergence) delirium, an acute confusional state that occurs as the patient awakens from ECT, is characterized by agitation, restlessness, clouded sensorium, disorientation, and failure to respond to commands. When postictal delirium is severe or persistent, it requires termination with intravenous diazepam.

Sackeim et al. (1) reported two patients who manifested postictal delirium after bilateral ECT and right unilateral ECT but not after left unilateral ECT. These authors hypothesized that ECT-induced postictal delirium reflected disruption of right-sided cerebral systems consequent to heightened neurometabolic activity in the electrically stimulated hemisphere. Daniel (2) claimed nonspecificity for the syndrome when he reported the contradictory case of a patient who developed a postictal delirium after bilateral ECT but not after right unilateral ECT. Recently, we (3) reported the case of a fully dextral patient who developed delirium after left unilateral ECT; we concluded that it was premature to attribute postictal delirium solely to right hemisphere mechanisms. Since then, we have systematically monitored the postictal course of all patients participating in a continuing study of ECT, and we now report seven additional patients who exhibited postictal delirium.

METHOD

All patients were fully dextral men who received a research diagnosis of melancholia consistent with *DSM-III* criteria and were randomly assigned to receive either bilateral ECT, left unilateral ECT, or right unilateral ECT for the first six treatments. Informed consent was obtained from each patient. When clinically indicated, additional ECT treatments were given after the sixth, and electrode placements were changed for the seventh and eighth ECT treatments according to a standard protocol. Treatments after the seventh were administered with bilateral ECT. After patients were premedicated with glycopyrrolate, methohexital, and succinylcholine, seizures were induced with a Thymatron brief-pulse instrument set to deliver a fixed stimulus of 378 millicoulombs.

CASE REPORTS

In each case, the delirious state began with motor restlessness during the patient's emergence from anesthesia and was initially characterized by automatic behaviors (e.g., picking at the sheets) that inexorably progressed to frank agitation that was unresponsive to reassurance or commands and necessitated manual restraint. The sensorium was clouded, speech was characterized by perseveration and non sequiturs, and comprehension was markedly impaired. In each case, we attempted to treat the delirious state with intravenous diazepam; however, in three instances, the patients' agitation and aimless thrashing about dislodged the intravenous line and attempts to reestablish it were unsuccessful. These patients were manually restrained until their delirium subsided, usually over a period of 15–20 minutes.

Delirium After Bilateral ECT

Case 1. A 48-year-old man awakened from his first ECT treatment in a pleasant, jovial mood and was immediately able to converse without difficulty. Emerging from his second treatment, however, he became restless and uncooperative and pulled out his intravenous line. Two attempted intravenous injections of diazepam each infiltrated, and six staff members had to restrain him throughout a 30-minute postictal delirium. Intravenous diazepam was administered after each subsequent treatment, and no further delirium occurred.

Case 2. A 34-year-old man recovered uneventfully after his first ECT treatment but developed delirium after his second. Intravenous diazepam rapidly aborted the delirium and was

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used successfully for this purpose after each subsequent seizure.

Delirium After Right Unilateral ECT

Case 3. After his first ECT treatment, a 34-year-old man developed delirium, which responded promptly to diazepam; subsequent treatments were successfully managed with prophylactic postictal diazepam.

Case 4. A 56-year-old man exhibited the same pattern of response as the patient described in case 3.

Case 5. A 62-year-old man became restless after his first ECT treatment but responded to reassurance and minimal physical restraint. After his second treatment, however, he became increasingly agitated and unresponsive to verbal commands, thrashed about aimlessly, and dislodged his intravenous line. Thereafter, he was given intravenous diazepam after each treatment, and no further delirium occurred. For the seventh treatment, the unilateral electrode placement was switched to the left hemisphere. Diazepam was withheld on this occasion, and he again became delirious. He was totally unresponsive to commands and required physical restraint until diazepam could be given, which rapidly terminated the delirium.

Delirium After Left Unilateral ECT

Case 6. After his first ECT treatment, a 60-year-old man developed delirium, which responded to diazepam.

Case 7. A 30-year-old man initially received right unilateral ECT but was inadvertently switched to bilateral ECT on the third treatment; his recovery from each of the first three treatments was unremarkable. According to the protocol for patients whose electrode placements were switched, he next received left unilateral ECT; on emerging from anesthesia, he became delirious, pulled out his intravenous line, and had to be restrained. Before another line could be restarted, the delirium began to subside and diazepam was withheld. The rest of his recovery was unremarkable. After the fourth treatment, he refused further ECT.

DISCUSSION

The hypothesis that ECT-induced postictal delirium is due to disruption of mechanisms lateralized to the right hemisphere (1) is not supported by our data. Including the patient from our previous report (3), we have now observed nine instances of ECT-induced postictal delirium in eight patients, distributed among all three conditions of electrode placement: bilateral ECT (N=2), right unilateral ECT (N=3), and left unilateral ECT (N=4).

Once a patient develops postictal delirium, it is our usual procedure to administer diazepam after each subsequent treatment. Thus, in most cases, it could not be determined whether patients who became delirious with one particular electrode placement would also have developed delirium after receiving treatment with a different electrode placement.

In a recent study that used a low-dose titration procedure to determine the seizure threshold, Sackeim et al. (4) calculated the mean seizure threshold in a mixed sample of male and female patients to be 154.31 millicoulombs (range=36–459 millicoulombs). Therefore, the substantial, suprathreshold amount of charge used in our study (378 millicoulombs) might have obscured lateralized postictal effects that would have been observed at a lower dose. The experience of our patient 7 militates against this possibility, as he developed delirium after left unilateral ECT but not after right unilateral ECT or bilateral ECT, all given with the same 378-millicoulomb stimulus. Moreover, the second patient of Sackeim et al. (1) did not receive titrated low-dose stimulation but, nonetheless, exhibited a markedly different emotional response to left unilateral ECT than to right unilateral ECT.

We agree with Daniel (2) that the most parsimonious interpretation of the data thus far on postictal delirium is that it is a randomly occurring phenomenon unrelated to lateralized hemispheric mechanisms.

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Prevalence of Clinically Significant Depressive Symptoms in Black and White Patients in Family Practice Settings

William W.K. Zung, M.D., James MacDonald, M.S., and Elizabeth M. Zung, B.A.

The authors administered the Zung Self-Rating Depression Scale to 764 black and 773 white adult outpatients in primary care settings. There was no significant difference between the races in prevalence of depressive symptoms or distribution of symptom severity levels.

(Am J Psychiatry 1988; 145:882–883)

Research findings to date have disagreed on the relationship of race to the incidence and/or prevalence of depressive disorders and their symptoms. One body of literature (1, 2) indicates that blacks have a lower prevalence of depression than whites. A second body of literature (3–5) suggests that blacks display a higher prevalence of depressive disorders and their symptoms than whites. After reviewing the current literature on depression and race, Neff (6) generated the hypothesis that racial differences in depression may be more pronounced when severity, rather than simple occurrence, is taken into consideration. A third view (7, 8) is that there is no significant relationship between measures of depression and race.

The purpose of the present study was to determine if there are any differences in depressive symptoms between blacks and whites studied with a standardized rating scale in family practice settings.

METHOD

The data used in this analysis were obtained at two large primary care settings in Durham, N.C. One of the facilities primarily treated white patients and was affiliated with a major university, while the other facility mainly treated black patients in a private practice setting. No formal data on socioeconomic status were collected, but both facilities serve an urban population composed of lower- to middle-class patients. All of the patients included in the study presented themselves to their physicians with physical complaints or ailments. Consecutive patients were screened for 1 year at both of the settings.

These medical outpatients were administered the Zung Self-Rating Depression Scale (9), a 20-item patient rating scale that provides an index of severity of illness from 25 to 100. Comparison of the operational definition of major depression as found in *DSM-III* and the Zung scale items demonstrated its content validity (10). A Zung depression index of 50 and over is used to screen for minimal or greater symptoms of depression, while an index of 60 and over correlates with symptoms of moderate or greater depression. The patients were asked to rate how they felt "during the past 2 weeks."

RESULTS

A total of 1,537 patients were screened at the two settings, 764 blacks (209 men and 555 women) and 773 whites (272 men and 501 women). The mean±SD depression index for blacks was 39.0±5.9, and for whites it was 42.7±9.5. Statistical analysis with a two-tailed unpaired t test showed no significant difference ($t=1.07$, $df=1,535$, n.s.) between the means of these two groups of patients.

To investigate possible proportional differences in the severity of symptoms, the depression indexes were divided into three categories: below 50, 50–59, and 60 and above. These are equivalent to the clinical global impressions of no clinically significant symptoms, minimal to mild depression, and moderate to severe depression, respectively. Table 1 shows the results, and it shows no significant difference in the distribution of severity levels between blacks and whites ($\chi^2=0.57$, $df=2$, n.s.). The proportions of subjects with no depression, minimal to mild symptoms, and moderate to severe symptoms were 77%, 17%, and 6%, respectively, among the blacks and 79%, 15%, and 6% among the whites.

The 1-year period prevalences of depression were 23% and 21% for blacks and whites, respectively, when the criterion used was minimal or greater depression (Zung depression index of 50 or more) and 6% for both blacks and whites when the criterion used was moderate or greater depression (index of 60 or more).

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TABLE 1. Depression Severity Levels of Black and White Outpatients in Family Practice Settings

Age (years)	Subjects With Given Severity of Symptoms (based on Zung depression index)		
	None (<50)	Minimal to Mild (50–59)	Moderate to Severe (≥60)
Blacks	587	130	47
18–24	31	11	8
25–34	100	27	9
35–44	68	14	2
45–54	94	23	6
55–64	116	24	8
65–74	131	21	11
≥75	47	10	3
Whites	614	115	44
18–24	99	16	5
25–34	234	39	9
35–44	96	18	5
45–54	58	16	9
55–64	62	15	8
65–74	45	5	5
≥75	20	6	3

DISCUSSION

Several problems associated with research on the relationship between depression and demographic variables are apparent from review of the literature: 1) variation in the method by which a case is defined, 2) lack of uniform definitions of the degrees of symptom severity, and 3) lack of a standardized instrument for measuring depressive disorders. By using a standardized scale based on an operational definition, with delineated limits for the levels of illness severity, in this study we were able to overcome these methodological issues. In almost all of the studies reported earlier in which blacks appeared to display a greater prevalence of depressive symptoms than whites (3–5), these differences disappeared when demographic and socioeconomic factors were controlled for. Neff (6) found that although mean level of depression did not differ between races when socioeconomic variables were controlled, there was a greater proportion of blacks who were more extremely depressed. We found no difference in the prevalence of depression but also found no difference in symptom severity.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

PSYCHOANALYSIS

Psychoanalytic Practice, 1: Principles, *by Helmut Thomä and Horst Kächele; translated by M. Wilson and D. Roseveare. New York, Springer-Verlag, 1987, 403 pp., $49.50.*

This book is quite expensive, but it is worth every penny. The focus of the book is on the psychoanalyst's contribution to the therapy process; in the opinion of the authors, who are German psychoanalysts, the psychoanalyst influences all aspects of the treatment continuously. The book also presents the special ambiance of psychoanalytic psychotherapy and psychoanalysis in postwar Germany. This is definitely not a book for beginners. It is quite scholarly and some of the sentences become additionally difficult in translation. It assumes a considerable knowledge of the field and a substantial acquaintance with the psychoanalytic literature. However, for advanced therapists it is remarkably provocative and always interesting. The authors manage to bring up almost every currently controversial topic in the field.

One is not surprised in a German text to find the subject of interpretation as hermeneutics and the work of Gadamer mentioned early in the book. But the authors show only a passing acquaintance with continental philosophy and at times seem unaware that the hermeneutic approach to knowledge cannot easily be integrated with scientific empiricism.

The first chapter of the book is the most difficult and probably the most provocative. Parts of it are quite dense and would have benefited from elaboration. For example, in their review of metapsychology the authors state, "Our own studies have convinced us that Rapaport and Gill's (1959) interpretation of metapsychology and its position in Freud's work is evenhanded, giving equal weight to the various metapsychological points of view" (p. 21). They do not elaborate on the 1959 view of Rapaport and Gill (1), apparently assuming that the reader is familiar with this difficult paper.

Remarkably, they view the work of Popper and Eccles, presented in a far-out book published in 1977 (2), as valuable for psychoanalysis. It is doubtful that many readers are familiar with the speculations of Popper and Eccles, and even if they were they would probably not agree with that fanciful point of view. Thomä and Kächele call on it because they hope to reject Freud's "materialistic monism" and to drop Freud's theory of instincts, which they regard as "mythology."

A crucial orientation of this book, presented in chapter one, is how the psychoanalyst's preliminary theoretical conceptions influence his or her listening and actions. Similarly, for these authors, psychoanalytic interpretation in practice is "embedded in a network of supportive and expressive techniques" (p. 41) that cannot be separated from it.

Although the authors are well acquainted with the different psychoanalytic theories, they state without evidence, "We believe we are justified in speaking of *convergences* between the different schools within psychoanalysis and also between psychoanalysis and neighboring disciplines" (p. 44). Certainly this will be a much disputed statement. In fact, some might argue that these schools and theories are diverging and polarizing rather than converging.

An interesting description of the different concepts of the baby from different theoretical models is presented in the first chapter, but the authors reject both Kohut's baby and Klein's baby because they claim that Kohut's baby is based on Freud's theory of narcissism and Klein's baby is based on Freud's theory of the death instinct—that is to say, both are based on "instinct mythologies."

The remainder of the book deals with different aspects of the psychoanalytic process. There is not enough space in this review to cover them all so I will mention only the most salient points that impressed me. In their discussion of the transference and emphasis on beginning interpretations with the here and now, the authors are in agreement with the views of Gill and Hoffman. Their approach to countertransference is not far from the ambiance of Kohut's self psychology; they believe that the patient should always be able to depend on the analyst's humanity and they object to the Kleinian idea that all countertransference is placed in the therapist by the patient.

Chapter four, on resistance, is the most controversial and interesting discussion in the book. It begins with the authors' contention that the analyst must always ask, "What am I doing that causes the patient to have this anxiety and provokes this resistance?" and "What do I do to contribute to overcoming this resistance?" The authors stress what they call the "interactional" aspects of the psychoanalytic process throughout the book. They believe their stress on the interactional aspects is much deeper than Sullivan's interpersonal theory, which, they say, neglects intrapsychic factors and does not recognize that the analyst's "participation" constitutes intervention from the very beginning of treatment.

Their view also requires an abandonment of the death instinct. They believe that the focus on the study of the negative therapeutic reaction leads away from the death instinct and to their interaction theory, which is based instead on the patient's need for mastery and autonomy. There is a fascinating discussion of the Holocaust (p. 126), which the authors (correctly, in my opinion) claim has contributed to the revision of the psychoanalytic theory of aggression. They contend that human aggressiveness and destructiveness lack the features of an instinct because there is no organ, energy, or object involved—a view they attribute to Anna Freud. Their point is that aggression is reactive and that what is central to understanding it is the degree to which the individual is personally affected or feels injured. Aggression for Thomä and Kächele is beyond biological explanation. National aggression involves regarding groups of target humans as subhuman, made so with the aid of propaganda.

In attempting to reformulate the psychoanalytic concept of aggression the authors lean heavily on what they regard as "a differentiated phenomenological and psychoanalytic analysis of the situational origin of aggressive impulses and fantasies"

(p. 128). They conclude from this analysis that human destructiveness is a correlate of self-preservation, an extreme extension of Freud's concept of self-preservation. When individuals feel threatened by the target of their aggression they feel they must wipe out the "enemy" in order to survive. This is a more extreme view than Kohut's concept of narcissistic rage. Kohut's work would be subsumed under it, but the authors stress a reactive element in the fear of threats to the self because of the regressive increase in fantasies of grandeur, which they say accompanies the danger posed by imagined enemies. This produces a vicious circle that transforms imagined enemies into more and more dangerous opponents who must be destroyed for survival. The purpose of this theory is to remove the death instinct as a postulated source of aggression, but, opposing Kohut, the authors view aggression as more fundamental than a breakdown product of normal assertiveness.

The technical consequence of this theory is very important, since it implies that the more insecure the patient feels in the psychoanalytic session the more aggressive and negative the transference. Thus, again, for Thomä and Kächele the transference begins and is centered on the here and now. In agreement with Kohut, they believe we must identify the perceived injury in the here and now and relate it to the childhood injury and consequent revenge fantasies. But they go beyond Kohut in their concern over omnipotent fantasies that arise interactionally—as a consequence of the childhood powerlessness induced by regression in the psychoanalytic situation.

The authors criticize Kohut because they feel that his notion of self-disintegration requires much more explanation, and they appeal to Erikson's notion of "identity resistance." Although they realize that Kohut's and Erikson's theories are based on different conceptions, they maintain that self-feeling and identity "can hardly be differentiated phenomenologically" (p. 135). What the authors have done in this text is to try to integrate the traditional psychoanalytic approach and the continental phenomenological approach in order to decide which psychoanalytic theories are best applicable to the actual technique and practice of psychoanalysis. They promise a second volume of case examples to illustrate their principles.

The same definitive interactional viewpoint applies to other chapters, such as those on the interpretation of dreams, on rules, and on process. For example, the authors maintain that research has proven Freud's view of dreams as the guardian of sleep to be wrong. They oppose "evenly suspended attention" as a myth based on an epistemological weakness in Freud's thinking as well as a lack of realization that perception is always theory laden and always involves explanatory models. They regard Reik's notion of the "third ear" and Bion's approach as mystical. They fall back on the need for mastery rather than Freud's id resistance or death instinct as an explanation of working through.

A very difficult chapter in the book is on models of psychoanalytic process. This includes the interesting Ulm model followed by the authors, in which transference is seen as an interactional representation. This model is carefully and lucidly presented. In the progress of the text the authors move farther and farther away from traditional Freudian psychoanalytic theory and deeper and deeper into their own model of psychoanalytic process, which they feel constitutes an advance over Freud and subsequent psychoanalytic theorists.

In the final chapter they conclude that psychoanalytic knowledge is acquired in a hermeneutic circle, but they insist that truths which are "dyad-specific" and acquired in the hermeneutic circle must then be tested as they are applied in the psychoanalytic process and putatively produce effective cures. Their emphasis on the testing of effectiveness of psychoanalytic treatment by research scientists is consistent with their discussion of the situation of psychoanalysis in Germany, which is supported by third-party payment plans. In that sort of medical system these processes must be empirically demonstrated to be effective in order to convince the agencies that pay for them of their value.

At the same time, the authors straddle both sides of the fence between a hermeneutic approach to psychoanalysis and an empirical approach, mixing together Gadamer, Habermas, Ricoeur, Eagle, and Grünbaum without sufficient realization, in my opinion, that these authors strongly contradict each other and claim that their orientations exclude those of their opponents. Either Thomä and Kächele do not have a sufficiently deep understanding of these continental and scientific points of view or they have glossed over some of the striking discrepancies between different conceptions of what constitutes psychoanalytic truth and how the results of psychoanalysis are to be validated.

Thomä and Kächele are to be congratulated for producing an interesting and important book that stimulates the reader on every page and survives translation at least to the point where their basic conceptions are not hopelessly lost. The book is highly recommended for advanced students of the subject.

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Freud and the Rat Man, *by Patrick J. Mahony. New Haven, Yale University Press, 1986, 241 pp., $23.50.*

Patrick Mahony's bold and imaginative analysis of Freud's analysis of the Rat Man proceeds, like the original, on multiple levels and tracks that reflect each other. Taken all together they create fascinating revelations of Freud, the 1907 Rat Man case, and the topic of obsessionality, which is shown here to have touched both participants. The enormous importance of the case is highlighted by the fact that Freud published only five full case histories, and the Rat Man is the only successful therapy directly treated and written by Freud. It provides the cornerstone for all his subsequent theories of obsessional neurosis and contains an exposition of most of the defense mechanisms of obsessionality known to this day. In addition, it was here that Freud differentiated primary from secondary defense maneuvers, and the structural theory, not formally proposed until 1923, is clearly identifiable. Mahony's reminder that Freud tackled the uncharted territory of Rat Man's complex and mystifying illness virtually alone helps the reader fully appreciate the stunning creativity of Freud's accomplishment and hold in proper perspective the flaws of his work, illuminated now with the brilliance of 80 years of collected hindsight.

Mahony first identifies the Rat Man and provides a detailed biography that enables the reader to follow his reconstruction of the analysis; this is a brilliantly detailed formu-

lation. Mahony synthesizes broad sweeps of dynamic reconstruction with particles of linguistic analysis. His microscope reveals the lake in a droplet, a panoply of anal erotism in the minutia of a grammatical construct. He also shows that Freud exaggerated the length and depth and thoroughness of Rat Man's analysis, probably to promote the cause of his new science. Although Freud said that the analysis lasted "nearly a year," Mahony reveals that regular and frequent sessions took place for little more than 3 months and then the work continued irregularly and infrequently for another 7 or 8 months. A textual analysis shows how Freud chose words and phrases that suggested a much slower and more gradual analytic process than was, in reality, possible.

The Rat Man improved dramatically in consequence of his analysis, but this cannot have been on the basis of resolution of his transference neurosis or a true working through of achieved insights, as Freud claimed. This becomes especially apparent when Mahony examines Freud's technique and differentiates his theory from his practice. In truth, Freud had little interest in therapy, and in his clinical work he was impatient and patriarchal. The Rat Man's "cure" was clearly a transference cure in response to the reassuring authority who explained, praised, encouraged, and gratified his passive patient. But all things considered, it is remarkable how much improvement took place. The analysis worked, but not for the reasons Freud gave.

Next Mahony tacks into the textual and linguistic analysis of Freud's work. He explores the influence of the oral-aural tradition. The written word differs radically from the experience of the spoken word, and Freud was a speaker who left indelibly powerful impressions when he spoke. Even his memory was phonographic, and he could reproduce verbatim accounts of lectures he had heard. Mahony shows a vast area that has been ignored in our science—the influences of sound and the transforming, constricting effect of writing that which has been spoken. Writing leads to abstraction and to formal deadness, made worse for Freud's readers by Strachey's "standard" translation. Throughout the book the limitations and taming influences of Strachey's work are noted. Mahony's judgment is severe: "When one studies Strachey's annotation (of Freud's process notes, for example) the term 'Standard' becomes more and more a glaring misnomer" (p. 21). Strachey sanitized Freud.

Freud recognized that Rat Man's verbalized obsessions split affect from meaning, and he deprived the obsessions of their despotic force by sounding them out and making them "experience-near." Thus he afforded his patient the stance of analytic comprehension and self-reflection, an agency that we have come to know as the observing function of the ego. Mahony goes on to review the progression of Freud's theories of obsessional psychopathology in detail. As early as 1906 Freud saw the origins of orderliness, parsimony, and obstinacy in anal erogeneity of early childhood, but he delayed spelling out that discovery until 1913. There had been much public derision of Freud's ideas on anal erotism expressed in the 1905 paper "Three Essays on the Theory of Sexuality." But that is not all. Freud complained of his great difficulty writing this case, and indeed the paper is disconnected, fragmentary, and aphoristic. Mahony argues that these problems, as manifestations of his own obsessionality, his countertransference, and the inevitable limitations of his self-analysis, reflect Freud's overinvolvement with the Rat Man. Mahony's reconstruction is that Freud had not yet discovered the essence of obsessional neurosis to be a regression from oedipal conflict to anal erotism; therefore, he remained vulnerable to a return of his own repressed mental contents. In an argument not totally devoid of obsessionality itself, Mahony links the defensive isolation of obsessionality with mental representations of the anal aperture. Lack of connection is rife in Freud's writing style, but so is its opposite—a concordant "processiveness" that connects disparate elements with each other and with realms of experience.

At the beginning of the book Mahony states his aim: "to write a coherent narrative enlightened by a synthesis of psychoanalytic, historical, literary, and textual approaches." No mean feat. At the end he extends that goal: "By the joining of ourselves as readers with Freud as clinician and author and with his patient . . . and by the interfusion of subject and object . . . Freud's own processes become the matter of [our] investigation." He has succeeded on both counts and made the enterprise fine reading in the bargain. In 1909 Freud revealed the Rat Man. In 1986, with Mahony's scholarly assistance, the Rat Man revealed Freud.

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PSYCHOTHERAPY

On Being a Therapist, *by Jeffrey A. Kottler. San Francisco, Jossey-Bass, 1986, 163 pp., $19.95.*

The perils facing a psychotherapist in life and practice—broken marriage, being seduced or sued, substance abuse, suicide or homicide—have been well publicized. The occupational hazards of a psychotherapist, including boredom and burnout, self-deception, and the phenomenon of one-way intimacy, have been noted in connection with patient treatment in the clinical literature. In *On Being a Therapist,* however, Jeffrey Kottler, a warm and articulate psychologist, intimately describes these hazards and then gives empathic advice to therapists on how to prevent and to cure them.

In a major section of the book, the symptoms of burnout, a common consequence of practicing psychotherapy, are described: the therapist's daydreaming and escapist fantasy; multiple clients complaining of hopelessness, frustration, pessimism, and doubt in the psychotherapeutic process; sessions losing their spark, excitement, zest, and spontaneity; and the therapist's feeling reluctant to call the office or to return calls, feeling excessively relieved when a client cancels, falling behind in billings and paperwork, being unwilling to discuss work in social and family circles, showing a clear preference for passive entertainment, feeling that the alarm clock is less a signal to begin the day than an order to resume his or her sentence, and manifesting cynicism about therapy.

Kottler describes the causes of burnout and then, in a personal and pragmatic fashion, sets out its prevention and cure. His easygoing and convincing suggestions for prevention are in essence to perform therapy differently, to teach others, to take personal responsibility, and, finally, to confront the source of stress.

The chapter on "Lies We Tell Ourselves" includes some lies that are necessary and others that are therapeutic, taking up the games therapists play as well as the myth of neutrality. According to this myth, the psychotherapist is expected not to engraft his or her own values on the client or even to represent, by actions or words, that values are a good thing. (In past times, this phenomenon of fibbing was noted by Epimenides, who said that all Ephesians are liars; it was discovered, however, that Epimenides was from Ephesus.) In

Kottler's book, the therapist's question of to lie or not to lie is proposed with warmth and with grace, making it easy for the reader to decide.

On the therapist's making errors, Kottler writes, "Although it is laudable to work toward greater consistency in the way we treat clients, a therapist is a fallible human being, one who is subject to quirks, biases, errors, misjudgments, and spectacular distortions of reality. Even with the best education, training, supervision, study, and self-analysis, a therapist is hardly the anonymous, perfectly stable, neutral, all-knowing and accepting creature that clients prefer to see."

Kottler discusses risking and intimacy as features of the transference in psychotherapy with humane, rational respect for both parties in the relationship. Discussing the transference, he personally and warmly reports a positive solution to the ubiquitous struggle between psychotherapist and client for power and influence. He also discusses the countertransference in difficult cases as well as the rewards of a psychotherapist's practice and closes with a stimulating chapter on creativity.

This is a how-to book, written for psychiatrists, social workers, family counsellors, psychologists, psychiatric nurses, and mental health technicians who practice long-term psychodynamic therapy. It is well written and attractive in format. Because of its excellent substance and charming style, I recommend this book to mental health therapists.

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Handbook of Psychotherapy and Behavior Change: An Empirical Analysis, 3rd ed., *edited by Sol L. Garfield and Allen E. Bergin. New York, John Wiley & Sons, 1986, 886 pp., $95.25.*

The important questions in the field of psychotherapy—How effective is therapy in general? How effective are specific techniques such as cognitive, marital, or brief therapy? What are the mechanisms of therapeutic change?—are discussed in this edited volume by well-known researchers. This *Handbook* offers comprehensive reviews of a vast literature that will be welcome to specialists in psychotherapy research as well as to readers who want an overview of the field or want to keep abreast of the latest research findings in a particular area.

Limited space precludes a comprehensive examination of a wealth of material contained in 19 chapters and organized within five sections; I will therefore highlight some of the more important material. The first section covers historical, methodological, and conceptual foundations of psychotherapy research. An introductory chapter by the editors discusses current trends in the field, including the growth of brief therapies, the development of treatment manuals, the concern with efficacy and cost effectiveness, and the lack of demonstrated superiority of outcome for any particular therapeutic technique. A chapter by Kazdin covering research design provides an excellent overview of issues involved in planning and evaluating empirical studies.

Reviews of the literature on the process and outcome of psychotherapy are contained in the second section. Strong empirical evidence for the effectiveness of psychotherapy is supplied in a chapter by Lambert, Shapiro, and Bergin. They review the evidence accumulated in more than 475 controlled studies demonstrating that at the end of psychotherapeutic treatment, the average patient is better off than 80% of untreated individuals. Research suggesting that treatment gains are more likely to be maintained if patients attribute change to their own efforts and if the therapist helps them to anticipate how they might react to crises and relapses in the future is also reviewed.

The relationship between the process of psychotherapy and the outcome—a research area of considerable relevance to the practicing clinician—is reviewed in an excellent chapter by Orlinsky and Howard. Their summary of the literature identifies a large number of therapist and patient influences on outcome, only a few of which can be mentioned here. Therapist confrontation, interpretation, and exploration were often associated with positive outcome, whereas reflection, advice, and self-disclosure had little differential effect on outcome. Additional therapist interventions that proved effective were focusing on affect and reactions to the therapist. Patients who exhibited greater immediacy of affective expression and who were open and nondefensive had better outcomes. The authors suggest that, to be maximally effective, therapeutic interventions require an "open" state in the patient which both influences and is influenced by the nature of the therapeutic bond. They conclude their exhaustive review of the literature with a comprehensive model of psychotherapy that recognizes the complex interaction between patient and therapist in producing a positive outcome.

Section three covers behavioral and cognitive therapies. The effectiveness of behavior therapy in the treatment of a variety of disorders is reviewed by Emmelkamp. He points out that even though behavior therapy is thought of as being very technique oriented, recent studies have shown that in behavior therapy as in the verbal expressive psychotherapies the therapist's qualities are more related to the outcome than is the treatment technique. The application of cognitive therapy to depression and other disorders is addressed in a chapter by Hollon and Beck. The field of behavioral medicine, including studies on the Type A personality and compliance with medical regimens, is also reviewed.

Section four examines research on children, adolescents, couples, and families. Gurman, Kniskern, and Pinsof review the effectiveness of the marital and family therapies for different disorders. The field of brief therapy is reviewed in an excellent chapter by Koss and Butcher. They describe the common technical characteristics of brief treatment and discuss the empirical literature on the process and outcome of short-term therapy. A review of pharmacotherapy by Klerman covers treatment for specific disorders as well as research that compares and combines drugs and psychotherapy. Other chapters cover group therapy, vocational counseling, therapy with the disadvantaged, and research on teaching psychotherapeutic skills.

The notable strength of this volume is the high quality of its comprehensive and up-to-date reviews of the literature. My major criticism has to do with the insufficient emphasis on psychodynamic treatment and issues. The editors deleted two excellent chapters by leading psychodynamic researchers that added enormously to the previous edition: an overview of the field by Strupp and a chapter on research on psychoanalytic therapy by Luborsky and Spence. In addition, in this edition references to psychodynamic therapy are scattered throughout the book rather than presented within one integrated chapter, as was done for the other theoretical orientations. Despite this flaw the excellent quality of the individ-

ual reviews allows this volume to retain its place as the best single guide to the empirical literature on psychotherapy.

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The Structure of Individual Psychotherapy, *by Bernard D. Beitman. New York, Guilford Press, 1986, 330 pp., $30.00.*

Dr. Beitman's motive for producing this book was to contribute to integration and systematic eclecticism in psychotherapy. He attempts to describe the common factors that define the nature of psychotherapy, dividing each psychotherapeutic relationship into four stages: engagement, pattern search, change, and termination. Each stage has characteristic goals, techniques, content, resistance, transference, and countertransference. Beitman concentrates on therapy, not theories of psychopathology. He believes we need no further schools of psychotherapy but, rather, a better sense of what we are doing. Because eclectics predominate among therapists, Beitman suggests that many therapists believe in a common (yet to be elucidated) base on which contributions of the different schools may be placed.

Beitman's search for commonality is motivated by the intent to liberate therapists from their dogma. But how many therapists wish to be so liberated? In my opinion, a therapist's favorite theory serves as a transitional object comforting him or her during times of separation from any possible clinical certainty. Although admirable from a scientific point of view, integration in psychotherapy seems to face as much resistance as does the clinical absorption of the findings of psychotherapy research itself.

Dr. Beitman wants therapists to recognize when they are making choices and to learn to understand their choices as functions of their personalities and therapeutic intent. He is forthright in citing examples from his own experience, including his errors as a therapist and why he once quit therapy as a patient. An example of failure to engage a patient comes from his report of his own rigid adherence to a structured research interview that led to the patient's fleeing to her family physician. He reports a countertransference dream and a period of sleep disturbance while he was treating a borderline patient and reveals how his failure to deal with the countertransference led to a hospitalization and unsuccessful termination of the psychotherapy.

In the pattern search section, Beitman applies seven different theoretical perspectives to the case of a man with bondage fantasies and a need to go to pornographic movies. Throughout the book, while he discusses a point of view he tells us what complementary notions other views can contribute. Eclecticism has its weaknesses, too, however. At times, Beitman presents comparative positions thinly, in a manner approaching name dropping.

The section on pattern search methods is particularly good and sophisticated, discussing listening, questions, and the linking of content to interventions. Beitman sees the patient's resistances to pattern identification as exceedingly useful because these resistances provide directly observable examples of key behavior patterns. He wisely reminds therapists that resistances, although very frustrating to them, usually represent the patients' best efforts at conforming to the expectations of therapy. Countertransference is particularly well discussed. Unfortunately, Beitman introduces but fails to clearly present the important work of Heinrich Racker on complementary and concordant countertransference. More exposition would have been welcome.

The book contains a lengthy section on change. Beitman takes us through the possible use of exhortation, interpretation, self-disclosure, the description of alternatives, modeling, direct instruction, and change facilitators. He claims that therapists use change techniques as a way to teach their own values and coping strategies. This is frequently true, and Beitman's volume does much to bring this to the reader's attention. That reader is most appropriately a resident or younger therapist whose identity as a therapist is still forming. More senior therapists might benefit from reading the book as well but are less likely to give it a try. Its richness lies in the large number of important aspects of individual psychotherapy discussed with plentiful clinical vignettes, a wide representation of recent psychotherapy literature, and an unabashed presentation of much of the author's personality and clinical experience.

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FAMILIES AND FAMILY THERAPY

Object Relations Family Therapy, *by David E. Scharff, M.D., and Jill Savege Scharff, M.B., Ch.B. Northvale, N.J., Jason Aronson, 1987, 494 pp., $40.00.*

There has been a regrettable but remarkably persistent antagonism between the fields of psychoanalysis and family therapy. Many of the early pioneers in the family therapy field have been psychoanalysts: Jackson, Stierlin, Bowen, Wynne, Lidz, and Fleck. Yet mutual enrichment between the two fields has been slow to develop. The family therapy movement flourished in a climate that was decidedly antimedical and antipsychoanalytic in its antipathy to the labeling of one member of a dysfunctional system as the patient. In psychoanalytic circles, focus on the family has tended to remain adjunctive and largely unacknowledged. Only recently have the two disciplines begun to approach each other and hold out the possibility of useful synthesis drawn from both fields.

Particularly useful for any efforts at such a synthesis of psychoanalysis and family systems thinking have been concepts drawn from object relations theorists, especially Melanie Klein, Wilfred Bion, W.R.D. Fairbairn, and Donald Winnicott. Klein's concepts of splitting and projective identification are the crucial bridges to a deep appreciation of the connection between archaic and unintegrated facets of the personality and the collusive transpersonal defensive operations that, in clinical practice, prove such stubborn obstacles to treatment. Bion's notion of containment—the empathic, tension-absorbing "reverie" that renders archaic tensions symbolizable, speakable, and "metabolizable"—adds a major contribution to the understanding of the therapeutic experience as one that enables individuals or families to gain control of their painful and unproductive cycles of repetitive symptomatic collusion and to move beyond them. Fairbairn evolved a schema for representing repetitive conflicts centered around internal objects. His schema, based on actual failures in the supporting environment, is well suited to conceptualizing work with families. Winnicott drew from Klein and Fairbairn to develop a unique view of the human predicament. He recognized both maturational processes and the facilitating human "holding" environment; his concep-

tualization of the therapeutic process has much in common with Bion's.

The profound, depth-psychological insights of these theorists have enriched family therapy with an expanded understanding of collusion and the nature of transpersonal defense, reactivity on the part of the therapist (countertransference) seen as a response to splitting and projective identification, and the phenomena of vicarious participation and repetition of pathological themes seen intergenerationally and intrafamilially. These developments have borne fruit. Recently, important efforts at rapprochement between psychoanalysis and family systems thinking have appeared in papers by Zinner and Shapiro and books by Sander (1), Box (2), Slipp (3), and Zilbach (4).

Object Relations Family Therapy is the latest and most comprehensive contribution to the synthesis of the object relations point of view with family therapy. The authors are prominent figures in the Washington School of Psychiatry's program in psychoanalytic family therapy, a program drawing from object relations theory, the group relations contributions of Wilfred Bion, family systems theory, psychoanalytic developmental psychology, and the pioneering work of Zinner and Shapiro on family psychopathology and treatment.

The book is Fairbairnian in its theoretical outlook. The authors state,

> The object relations approach to families provides emotional space for a rediscovery of each other and of the lost parts of the self that have been put into each other. These projected parts of the self may have been put into others for safekeeping, as in the case of the good part of the self that is threatened by one's hate, or for good riddance, as in the case of a hated and rejected part of one's self. The space we offer provides the basic safety for the family to sort out, modify, and re-introject projections in a metabolized form. Object relations family therapy works to understand these projections and the failures of the family's holding capacity that have resulted from and contributed to them. (p. 169)

As with any form of family therapy, symptoms are seen in the family context:

> The symptomatic individual may be viewed as holding a compromise between his individuation and the solidarity of the group. Symptomatic family patterns can also be viewed as a compromise between the family's goals and those of the previous generation. And symptom formation can be seen as a signal of anxious unrest in the family system, as it seeks and resists a new equilibrium appropriate to its current developmental phase. (p. 194)

The book has 19 chapters and is divided into five sections: an overview section; one on theory and development; one on technique, transference, and countertransference; a long section on specific life phases and predicaments of families coming for treatment; and a final section on terminations.

The foundation on which the book stands is less the authors' theoretical orientation than the elaborate and thoroughly first-rate clinical material, which covers a wide range of situations by no means confined to the Fairbairnian approach. Seldom have I read clinical material as empathic, mature, and psychotherapeutically credible as that which is consistently found in the pages of this encyclopedic work. This is one of the rare books on family therapy in which the reader is offered an opportunity to identify with patients and their families rather than with hypomanic and triumphant ploys and stratagems of therapists attempting to turn the tables on those they are supposed to help. Again and again, the Scharffs illustrate what frontline practitioners know very well: that family therapy, like any other kind of psychotherapy, emerges from an enduring relationship and not the short-term power plays so overrepresented in the family therapy literature.

The book is long and ambitious in scope. It is comprehensive enough to be a sourcebook for an entire curriculum, with detailed chapters on every phase of the family life cycle, contributions from psychoanalytic theory and from group relations, and detailed discussions of technique. The splendid final chapter on "endings" is one of the few thorough sources on separations in the family therapy literature. It underscores the Scharffs's emphasis on the family's meaningful relationship with the therapist that is found throughout the book.

The book is less strong on the strictly theoretical facets of object relations theory. In my opinion, the authors give a bit too much weight to Fairbairn's contributions and not enough to Melanie Klein's and Bion's. As a result, their case material is not quite so clearly connected to an understanding of the therapeutic process as it might have been if the Kleinian notion of projective identification and Bion's notion of "containment" in the therapeutic process had been more tightly linked with an understanding of the manifestations of splitting in the clinical examples. The volume would be more readable cover to cover with a bit of pruning. It is, nonetheless, the most important contribution on the interface between psychoanalytic family therapy to appear since Henry Dicks's epoch-making *Marital Tensions* (5) appeared in 1967. *Object Relations Family Therapy* is a major step forward in the maturation of the family systems point of view to include the skills and disciplines of a truly seasoned and caring psychotherapist. It should be considered alongside Dicks's work as a standard source in the field of psychodynamic family therapy.

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Children, Parenthood, and Social Welfare in the Context of Developmental Psychology, *by Michael Siegal. New York, Clarendon Press-Oxford, 1985, 162 pp., $26.95.*

This very interesting book is fun to read, but it is somewhat dangerous; it is written in a style that juxtaposes certain material and then subtly proceeds as if there were a cause-and-effect relationship between the material. While doing this the author also subtly and not so subtly criticizes

Freud and the medical model and sets the stage for his book to be a manifesto for a certain political persuasion relative to psychosocial economics. This book follows the author's 1982 publication on moral development (1). Drawing on studies of adults and children, Siegal, an Australian psychologist, examines development, the socioeconomic conditions of the family, parenthood, and parent-child interactions. Instead of a biopsychosocial analysis or a parent-adult-child analysis, there is a parent-child-social (i.e., the child outside the family) analysis that purports to result in an attempt to integrate theories of development. Indeed, it is the author's stated purpose to integrate theories of development toward a more complete understanding of the nature of the connections between child development and social welfare.

The children studied were 3–18 years old, spanning preschool, kindergarten, and 12 grades of schooling. The child data came from several national sources: Australia, Denmark, England, Japan, The Netherlands, the United States, and other non-Communist countries. About 400 references are listed.

The terminology of many disciplines is used, such as those of the justice system, sociological theories, and learning theory. Terms like Bronfenbrenner's exo-, meso-, and macrosystems as well as trickle down, bubble up, self-system, and self-definition are used. It appears there is a recoinage of terms such as Type A and Type B so that they involve deprivation. I did not notice direct acknowledgment of the contributions of psychoanalysis, but Freud and identification are discussed at some length in the second chapter, "Moral Development in Context."

This chapter begins to reveal the literary dilemma facing the reader. Although the professor of English may say that the progression of subjects and sentences is technically well done, one educational psychologist's assessment can only be paraphrased here by saying that the author does not write clearly and from this one can conclude he does not really understand his own material. A philosopher psychiatrist reading the following sentences expressed pity for the reader confronted with them:

> A boy's desire to identify with the father and command the attractive goals which the father possesses will give rise to an important consequence of this identification: an attempt to take on what are perceived to be the father's characteristics as often evidenced in sex-typed behaviour. While the content of identification as an acquired cognitive response can consist of similarity in overt behaviour between an individual and a model, such matched behaviour is not an all-or-none process and outward similarity may mask different motives underlying behaviour.

Although there are many sentences that are difficult to understand, the book stimulates many exciting and thought-provoking ideas. Perhaps the author tried too hard to be faithful to the language of his numerous sources and thereby produced a text that many times does not flow from sentence to sentence and often forces the reader to interpret the text. Nevertheless, if the author's own fallacious syllogisms are indications of his critical assessment of his sources and references, then the reader has fairly ample reason to doubt the accuracy of major portions of the book. Additionally, although I found it interesting that mother identification has been significantly associated with rule conformity in middle-class boys and father identification with rule conformity in middle-class boys and girls, I still wonder who started the idea that rule violating is associated with father identification, development of autonomy, and separateness. A better analysis might be that children who violate rules do so because they suffer from a lack of something (father input?) and therefore are adrift, as the author says.

In chapter three the reader becomes indebted to the author for illustrating that psychological and sociological research contain their share of flimsiness, and in chapter four one notes that mothers rather than parents are consistently cited in the studies on parents, peers, and children's appraisals of others' behavior. Chapter five, dealing with morality and criminal justice, also cites mothers rather heavily, along with laxity in control and permissive child rearing as the greatest prediction of a son's delinquency. This chapter notes Baldwin's maxim that children practice in the peer group what they learn from adults. A good case is made here that children themselves will tell you they misbehave (because they have no introjects related to propriety and impulse control) because one or both of their parents were lax in control and permissive (i.e., did not set limits); the children perceive this parental behavior as their parents' not caring enough to get involved with the work of parenting. The influence of free time as an opportunity to practice delinquency is cited too.

The chapter entitled "Achievement and Economic Justice" does little more than describe some logical differences between traditional and nontraditional Western families regarding distribution of income, while some apparently pertinent Japanese family and business relations are described. My question is, Is the "traditional family" in effect a misnomer, and is that which is called the "Western traditional family" in reality just a stage of family "phylogeny" that came under study in the middle half of the twentieth century?

The seventh chapter reviews the arguments as to whether conflict is beneficial and describes associations with the developmental stage of adolescence. The eighth and final chapter is somewhat of a summary; it also emphasizes studies about changes in family structure, how working mothers are now the majority and their numbers are growing, how the instability of the father is more a factor than whether mothers work, and how "there would seem to be no reason why fathers should not perform equally affectionate and warm roles and be every bit as 'motherly' as actual mothers." Several interesting ideas about conflict and child custody are discussed, and there is an excellent diagram of parent-child relations in a socioeconomic context. The author moves to his thesis that increasing revenue in private and public sectors will result in new jobs and assist "to provide a strong basis for family relationships." He thinks similar effects occur once children enter the workplace as adolescents and may be enhanced (presumably by government money) through family support programs. His thesis seems to assume that all other factors are either equal, and therefore discountable, or at least subordinate to monetary input. There is no study mentioned that assesses how any of these adolescents or even their parents spend the money available to them.

I think that the close relationship between delinquent behavior and low socioeconomic family status could be the result of some underlying CNS or ego defects. Each can in time exacerbate the etiological CNS or ego defects as well as one another. Child abuse would be likely to be more prevalent under such conditions and would be primarily a failure of impulse control, but I do not contend that medicine holds all the answers, as the author charges. Siegal would have had a scientific book if he had been less interested in making

social and professional political statements and used better composition techniques.

The best features of this book are the extensive bibliography of psychological, sociological, psychiatric, and developmental literature and the fact that Siegal succeeds in calling attention to the effect the child has on the psychosocial systems of family, workplace, and the nation.

Although I hope that no one will use this book as an authoritative basis for federal funding of social welfare programs, I do recommend the book as very interesting albeit somewhat difficult reading. Those who know little of any of the material discussed will either find it very difficult reading or will be completely charmed and use it as a manifesto.

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Family Resources: The Hidden Partner in Family Therapy, *edited by Mark A. Karpel. New York, Guilford Press, 1986, 479 pp., $37.50.*

The widening scope of individuals seeking treatment has resulted in a parallel widening of therapeutic alternatives in the mental health profession. As the nature of those seeking help has changed, the treatment modalities available have been modified, often without any acknowledgment of the way in which the new patient population has resulted in changes in technique and how these innovations relate to previous therapeutic techniques. The result, although undoubtedly beneficial for many seeking treatment (particularly if their problem connects properly with the therapist's school of treatment), has led to a surprising lack of connection between more recent pragmatic approaches to treatment and the earlier, more complex, and historically more developed therapeutic modalities. This is particularly true in family therapy as it relates to individual analytically oriented psychotherapy. Although much that family therapists do in their interventions with disturbed families is entirely understandable from the viewpoint of individual dynamics, many family therapists, rather than acknowledging a link to individual dynamic psychotherapy, have defined their work in terms that are often hostile toward and competitive with the intents of individual psychotherapy and psychoanalysis.

The editor of *Family Resources* and the contributors he has chosen are very much in the group of family therapists who disdain or lack interest in the history of psychodynamic understandings of the individual. Their lack of awareness of psychodynamically based psychiatry is shown in their choice of mentors: Milton Erickson, Boszormenyi-Nagy, Minuchin, Palazzoli, and Halley. Missing entirely is any direct or indirect reference to Freud, Sullivan, or any modern psychoanalytic or psychiatric thinker. In essence, the therapy described by the authors of this volume dates from the 1970s and has no connection with the work of previous psychiatrists.

Karpel expresses hostility to individual therapy in two ways. First, he simply doesn't mention that it has any role. Although this may be a small improvement over attacks on individual therapy by family therapists, it still fails to place family interventions in the proper perspective of individual development and treatment. Second, Karpel's emphasis on family resources seems to split family therapists into good and bad. The "good" therapist looks for strengths in the family system, and the "bad" therapist approaches a family in terms of defining the pathology within the family system. Viewing families as pathological is seen as destructive. Psychiatry and individual therapy, with their emphasis on defining and treating pathology, are the obvious target of this attack on the legitimacy of appraising the degree of pathology in a family.

All of the contributors to this book emphasize looking for what is positive in the families who consult them, no matter how horrendous the problems they bring. According to Karpel, family resources are "those individual and systemic characteristics among family members that promote coping and survival, limit destructive patterns, and enrich daily life." It would be hard to find any basis for disagreement with the suggestion that such qualities, if they exist in a family, should be sought out and emphasized in any family treatment process.

Karpel deemphasizes the pathology that can be clearly seen in the families he describes. The therapists who present their work and ideas in this volume all share an optimistic view of family life as well as what I would consider an inadequate appraisal of the nature of the separation and individuation process in the course of healthy individual development within a healthy family setting.

Almost all of the interventions described in this book are very brief. Even those which persist over a longer period of time tend to involve very few sessions with the families. These therapists avoid the emergence of the family members' pathology in the transference by keeping the contact short-term and work against resistance by allowing the family to determine the style, length, and depth of the therapy they receive. The result of treating a family based on the establishment of such a narcissistically based alliance is, as should be expected, often dramatic in its ability to modify behavior and reverse pathological regressions and enactments. This should not be confused, however, as it is by these authors, with any substantial increase in insight or fundamental change of the barriers to individuals' "right to a life of their own" within a disturbed family matrix.

Without the acceptance of pathology as the legitimate focus of psychotherapy, there is no perspective in evaluating what is wrong with the individuals in the family or what is the impact of the therapist's interventions. Thus, in many of the clinical examples cited by these authors, a very similar picture emerges:

A family or couple appears at the evaluation to be beset by the most overwhelming disturbances in several if not all of the members. The therapist's intervention is simple, often involving an intuitive reading of the level of intervention the family is able to use in some way. For instance, the therapist might tell an angry narcissistic husband that although his wife's request that he change is reasonable, he is incapable of ever changing. The husband reacts with angry disbelief and an attempt to prove the therapist wrong as quickly as possible. Thus, the response to therapy is a dramatic reversal of behavior and a rapid disappearance of disturbed behavior, a reversal that, depending on the establishment of a correct diagnosis, would, in fact, be close to miraculous.

The psychiatric reader has an obligation to be critical of the kind of material presented in this book; the denial of individual pathology in favor of a "systems" approach borders on the scientifically unacceptable. Repeatedly we are exposed to therapists who confuse their manipulative interactions with families, clever though these may be, with a real

understanding of interpersonal and individual dynamics. The interventions of the family therapists who present their work in *Family Resources* is undoubtedly based on a wish to be helpful, but their lack of connection with the basic tools of dynamic psychiatry makes their work appear superficial even when it is helpful. In addition, their claims of superiority for what they do over the work of individual and family therapists who emphasize the identification of psychopathology as essential for any effective psychotherapeutic intervention are both offensive and naive.

This volume needs to be read by those who keep track of the trends in the broad world of psychology and psychiatry. The antipsychiatry movement of the 1960s can be found alive and well in the group of family therapists presented here. Allowing blatant pathology to go unmentioned or uninterpreted as the price of forming a therapeutic alliance is a far cry from insisting that the pathological is benign or even adaptive. I can only recommend this volume for its clear presentation of so much that is wrong with family therapy when it derives from an anti-intellectual, anti-individual-treatment, suspicious view of individual dynamic psychotherapy. We must be vigilant in not accepting the ideas of those who attack and neglect clinical contributions that they find inconvenient.

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LAW AND ETHICS

Forensic Psychiatry and Psychology: Perspectives and Standards for Interdisciplinary Practice, *edited by William J. Curran, J.D., LL.M., S.M.Hyg., A. Louis McGarry, M.D., and Saleem A. Shah, Ph.D. Philadelphia, F.A. Davis Co., 1986, 535 pp., $49.00.*

This textbook deals with gripping subjects: sex, violence, madness, and making decisions to rip families asunder or bind them perilously together. Consequently, I was puzzled at first when I had to struggle to stay awake while reading it. The typical textbook is bland and boring, but this one shouldn't be. How can one nod off in the midst of such issues?

The problem is only in part the creation of the book's editors and authors. In fact, they are a distinguished group, and we are not likely to see a more authoritative treatment of forensic psychiatry in this decade. The best chapters—those of M. Kindred and B.D. Sales on the developmentally disabled, C.S. Widom on juvenile delinquency, L.H. Roth on psychiatry in prisons and jails, and W.A. Kennedy on expert testimony—are substantial contributions. The chapter by C.C. Nadelson, M.T. Notman, and E.(H.) Carmen on the rape victim is a significant broadening of perspective, one not to be found in older books.

The soporific effect of this book is largely a problem of dilution. The reader must sift through too many words to extract the nuggets of useful knowledge. The problem is not peculiar to this set of writers. It is an unhappy fact that in forensic psychiatry we do not know very much.

One symptom of insufficient substantive knowledge is the considerable padding of chapters with information from neighboring disciplines, as if there were not enough truly psychiatric and psychological knowledge to fill the pages.

Consider, for example, the several chapters on psychiatry and criminality. Sociologists have collected voluminous statistics on the incidence, prevalence, and correlates of misbehavior, especially criminal misbehavior. Judges and legislators have ground out millions of words on their side of the border between medicine and law. A textbook of forensic psychiatry needs some information from those neighboring disciplines, but only some. To be useful, a textbook has to concentrate on its own central subject. This the authors frequently do not do, and not because they are forgetful but because the primary research literature in forensic psychiatry is too thin. Thus, R.K. Gable's chapter on prediction of dangerousness reviews the sociological statistics at length but does not, because it cannot, cite much that might actually help a clinician to make a prediction (see, for example, the discussion by Curran and McGarry on pages 528–529). If Gable's chapter is of little help to the practicing clinician, it is not because he doesn't know the research literature but because he has mastered it and knows its limitations.

Many of the authors frankly acknowledge massive gaps in knowledge. On the question of whether psychiatric assessment of defendants accurately determines competence to stand trial T. Grisso and S.K. Seigel report that "the answer . . . is not known" (p. 161). A. Rosenbaum, writing on violence in the family, states that "our knowledge . . . is rudimentary and inadequate" (p. 228), and he goes on to condemn the "Woozle effect," which is especially endemic in the child abuse literature: "the repeated citing of the results of inadequate research studies until the findings attain the status of facts and the poor quality of the research is forgotten" (p. 233). As to therapy for violence in the family, Rosenbaum confesses that we know virtually nothing about what types of therapy work best, work not at all, or are even harmful (p. 242). Likewise, on a topic at the heart of forensic psychiatry, S. Dinitz frankly states, "Antisocial personality is a clinical disorder whose course, mechanism, and etiology remain unknown" (p. 391).

When the information quotient of writing is low, it is easy to write badly. A number of the authors have done so. For example, one finds such sonorous pontifications as, "Many of the ontogenic, microsystem, and exosystem factors are conceptualized as contributing to the production of marital discord" (p. 235). Deciphered, this turns out to be a platitude: married couples are unhappy for many different reasons. More often, the platitudes and tautologies are written in plain English, such as, "When there is poor agreement . . . between two persons . . . it is fairly certain that at least one of them is incorrect" (p. 133). And, "Studies have frequently reported the involvement of alcohol with aggressive crimes" (p. 139).

Even one of the longest and most scholarly chapters, S. Shah's discussion of the insanity defense, will be of only slight help to the practitioner who must evaluate a real defendant. Shah has done about as much as is possible with the available materials. The difficulty lies in the literature itself, which mostly chases the same set of abstract concepts around and around in philosophical circles without tying them to observable standards. In jurisprudence, equally abstract but necessary ideas have been given substance by the accumulation of thousands of published cases. The critical tort law boundary between "reasonable care" and "negligence," for example, has little meaning when stated abstractly. But judges have the benefit of case reports in which the issue has been decided on the basis of almost every conceivable combination of particular facts. This may be a bumbling, trial-and-error way for society to reach a consensus, but it does the job. In contrast, the psychiatrist who

confronts, let us say, his first ax murderer through the bars of the county jail has little more than guesswork for guidance if he or she wants to assess competence to stand trial and criminal responsibility by standards consistent with those of his or her peers and predecessors.

Some chapters seem to be insufficiently updated from a previous book (1). In particular, the chapter on the antisocial personality cites only one post-1977 source, and most of the citations are more than 20 years old. This chapter is perhaps the least satisfactory for other reasons as well. It presents one form of biological speculation on sociopathy, the autonomic excitability hypothesis, as if it were a reasonably well-established fact. This is one of only a few points on which the authors have overstated the certainty of knowledge.

One hopes that in a future edition the editors will tackle some important topics that the present volume slights or omits entirely: standards for civil commitment, malingering, testamentary capacity, guardianships, and conservatorships. A more practice-oriented approach also would make a more useful book. Consider questions like these: What should the psychiatrist ask a 3-year-old whose broken leg may or may not have been inflicted by her father? What should he or she ask the father? What facts should be considered in the wrenching but unavoidable decision to return that 3-year-old to her family or to place her in foster care? Such practical questions are seldom addressed—perhaps because no one knows the answers.

At least one chapter is as practical as one could desire and very well written as well. Wallace Kennedy's guide to giving expert testimony will benefit the seasoned professional as well as the novice. It contains, among other treats, perhaps the best single sentence in the book. Advising on preparation for a court appearance, Kennedy admonishes, "Take the time or don't take the case" (p. 503). If the entire book met the standards set by Kennedy, Widom, Kindred and Sales, and Roth, this textbook would be superior instead of adequate.

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A History and Theory of Informed Consent, *by Ruth R. Faden and Tom L. Beauchamp. New York, Oxford University Press, 1986, 381 pp., $29.95.*

In the medical ethics literature there are hundreds of citations on informed consent. Until now, however, no one has attempted the project the authors assign themselves in this book—the provision of a comprehensive history and theory of informed consent. That they are only partially successful, particularly in the theoretical section, is testimony to the near intractable difficulty of the task.

The book is divided into three sections, of which the first, chapters one and two, provides a clear introductory-level overview of the foundations of informed consent in moral and legal theory. It was somewhat surprising to read, however, at the conclusion of chapter one, the authors' aim for the book:

> We shall be arguing for the priority of enabling autonomous choice as the goal of informed consent requirements. However, we shall not argue that either this goal or the underlying principle of respect for autonomy always or even generally outweighs other moral duties or goals in either medical care or research.

Is this a becoming modesty, setting the lesser tasks of description and conceptual analysis and leaving the prescriptive work for others? It does not appear so, since later in the book it becomes progressively clear that the authors have definite ideas about how informed consent should be understood and used. Hence, their stated aim seems a bit disingenuous, as another reviewer (1) has already noted.

Section two, comprising chapters three through six, is excellent. Here is a thoroughly researched and lucid history of informed consent from Hippocrates to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1980–1983). Most striking in this history is the observation, which the authors note but do not fully explain, that before the late 1950s virtually nothing was written about nor was there substantial attention given to the issue of informed consent within the medical profession itself or in philosophical ethics. Only in the law were there earlier stirrings of concern for the requirement of consent. The authors observe that it is difficult even to read medical history before 1950 in terms of modern conceptions of informed consent because when patients' consent was solicited in earlier times it was justified on the basis of the patients' good rather than the patients' rights or autonomy.

The third and final section of the book, comprising chapters seven through 10, is the most ambitious and the most problematic. On close examination, the concepts of autonomy, autonomous actions, autonomous persons, and, ultimately, informed consent, are exceedingly difficult to precisely conceptualize. To their credit, the authors do not avoid these complexities by resorting to simplistic abstractions. In the real world of medical care, as they are aware, these terms must make some practical sense and be capable of operational definition if they are to have useful application. The fundamental problem is, of course, that Western thought has failed to develop a satisfactory theory of human nature. Are human beings free or determined, organisms or agents, subjects or objects? Is there some content to the concept of human good or is human good whatever an individual decides, no matter how arbitrary? Faden and Beauchamp encounter these issues again and again as they struggle with the definition of substantially autonomous action, the use of subjective or objective criteria in assessing levels of patient understanding, and their attempt to find some moral basis for physicians' use of persuasion while respecting the patient's autonomy. The authors take positions on each of these thorny questions but do so without establishing the validity of their point of view.

As they do, the reader cannot avoid being troubled by a recurring circularity. This circularity arises from the authors' attempt to fashion a conceptual analysis of informed consent to rationalize a previously assumed set of outcome conclusions. For example, the authors describe as "profoundly inadequate" and "tainted by an implicit assumption of medical authority" a definition of informed consent that emphasizes only the giving of information. They also describe as "discouraging" the results of a survey in which a popular answer to the question, What does the term informed consent mean to you? was that the patient agrees to treatment by letting the doctor do whatever is necessary, best, or whatever he sees fit. Further, in providing a critique of Miller's concept of au-

thenticity in informed consent, the authors argue that such a view "risks resulting in more physician unwillingness to accept patient refusals than would be morally acceptable." Readers will vary in the degree to which they assent to these "valuing" positions taken by the authors. But what seems odd is that the authors repeatedly use their already formed preconceptions of what is the good and proper conception of informed consent practice to drive their conceptual analysis, thereby reasoning backward from conclusions to premises. Precisely the reverse is what is most urgently needed—a conceptual analysis of informed consent that reasons forward from a theory of human nature to a plan of action that, by virtue of the analysis, is morally justified.

Finally, as a psychiatrist, I was troubled that after briefly considering a vignette of an obsessive-compulsive patient which, the authors admit, throws serious doubt on their whole conception of autonomous action, they go on to ignore its clear implication that their theory may require modification. So much for the needs of psychiatry. Nor was I heartened to read that "inducing of guilt or feelings of obligation" belong under the broad heading of "psychological manipulation." This I would have expected to read in a book in pop psychology but scarcely in a treatise on ethics.

Overall, this book can be recommended for those who would like a competent statement of the current status of the history and theory of informed consent. But it also has considerable potential as a stimulus to interdisciplinary collaboration. Especially for psychiatrists with theoretical interests, the book constitutes a possible conceptual bridge between psychiatry and ethics. Both disciplines require a theory of the person adequate to the needs of the times. Until now, neither psychiatry nor ethics has succeeded alone.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Use of Potassium to Treat Lithium's Side Effects

SIR: Animal studies (1–3) suggest that potassium may widen lithium's therapeutic index. We wish to report a clinical application of these animal data.

Ms. A, a 31-year-old woman with a 10-year history of cyclic mood disturbance that met the *DSM-III-R* criteria for mixed bipolar disorder, was referred for outpatient care following a brief hospitalization for an acute psychotic exacerbation. She was taking haloperidol, 30 mg/day, and benztropine, 4 mg/day, at that time. At admission to outpatient care, Ms. A exhibited rapid, pressured speech, flight of ideas, expansive, labile mood, and increased motor activity. Results of a physical examination were normal except for obesity (height=170.2 cm; weight=101 kg). An ECG taken during her hospitalization was normal, including T-wave form and height. Electrolyte levels were normal (sodium=141 mmol/liter, potassium=4.7 mmol/liter [sample partially hemolyzed], BUN=14 mg/dl, creatinine=1 mg/dl). Because the patient had responded favorably to lithium in the past, lithium, 1200 mg/day, was added to her therapy, resulting in a steady-state plasma lithium concentration of 0.6 meq/liter.

Ms. A gained rapid remission, but she suffered breakthrough depressed mood after 1 month's lithium treatment. Her dose of lithium was increased to 1500 mg/day, yielding a steady-state lithium level of 0.9 meq/liter, and her haloperidol was decreased to 20 mg/day. The benztropine dose was not changed. Her depressed mood resolved; however, during the 2 weeks following the increased dose of lithium, Ms. A developed a rapid, fine tremor in both hands and nonpitting ankle edema. Reduction of the lithium dose to 1200 mg/day eliminated these side effects, but it also resulted in the return of intermittent depression. Rechallenge with 1500 mg/day of lithium brought about euthymia but a return of the tremor and ankle edema as well.

Potassium, 16 meq/day (in slow-release capsules), was added to Ms. A's medications. The tremor and edema abated over 1 week, and lithium was maintained at 1500 mg/day. One week after the addition of potassium, the patient's steady-state plasma lithium concentration was essentially unchanged at 0.8 meq/liter (within test-retest variance in our clinical laboratory). Concurrently measured electrolyte levels remained normal (sodium=141 mmol/liter, potassium=3.7 mmol/liter, BUN=11 mg/dl, creatinine=1 mg/dl). Follow-up ECG data are not available. Ms. A remained euthymic.

Two months after beginning potassium treatment, Ms. A was instructed to discontinue the potassium while maintaining the doses of lithium, haloperidol, and benztropine as before. Lithium-induced tremor and ankle edema rapidly returned. Resumption of potassium, 16 meq/day, again resolved these side effects without disturbing her remission.

Our clinical observations do not provide data about the mechanism of potassium's apparent benefit to this patient. However, some plausible explanations can be considered. Lithium produces potassium wasting in the distal renal tubule (1, 2), which perhaps explains why potassium-sparing diuretics are particularly effective in treating lithium-induced edema. Additionally, spironolactone has been reported to show antimanic effects (4, 5), suggesting a possible role for intracellular neuronal potassium in bipolar disorder. Intraneuronal competition between potassium and lithium may underlie lithium tremor, much as lithium-iodine interaction produces hypothyroidism.

Understanding how potassium protects against lithium toxicity without interfering with treatment may give us new insights about lithium's therapeutic mechanisms. Thus, continued and systematic clinical investigation is important.

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The Charles Bonnet Syndrome and Grief Reaction

SIR: Charles Bonnet (1) described visual hallucinatory phenomena of a pleasant or neutral nature that occurred in elderly persons with sensory deprivation, for example, ocular pathology. His grandfather had vivid and detailed visual experiences that he knew were unreal. These occurred without signs of a dementiform process. Alroe and McIntyre (2) later described the Charles Bonnet syndrome in elderly women after the death of their spouses. Although there have been several reports of this syndrome in the European literature, there are only a few descriptions in the American literature (3, 4). We describe a patient in whom sensory deprivation predisposed her to visual hallucinations as a symptom of grief reaction.

Ms. A, an 85-year-old black woman, was referred for evaluation of hallucinosis and competency to care for herself. She had had no previous contact with a psychiatrist.

Her medical history revealed that she had become blind secondary to bilateral glaucoma 8 years previously. During the interview she was pleasant and cooperative. Her cognitive functioning was remarkably intact. She revealed that her son had died a month earlier. Since his death she had experienced nightly visions of him and other deceased relatives whom she would see in detail. There were no associated auditory hallucinations. She did not find these occurrences disturbing but instead seemed rather pleased by them. She was encouraged to talk about her losses and later was able to admit she grieved for her son. During a follow-up visit several weeks later, she expressed further distress over her loss. She reported that the visions had ceased.

Pleasant visual hallucinations in an elderly person with visual impairment and intact intellectual functioning conform to the description of Charles Bonnet syndrome. Visual hallucinations in this syndrome are thought to be "release phenomena" associated with sensory deprivation. In the case of Ms. A, in addition to sensory deprivation, the hallucinations may have reflected a compensatory recall of visual memory traces secondary to bereavement (2). This is supported by the observation that through grief work her hallucinations ceased. In this sense, the symptoms were not indicative of psychotic phenomena but may have represented a reparative process. Treatment with antipsychotic medications would thus have been both unnecessary and fraught with undesirable side effects.

Babcock (4) recently described the case of an elderly man with ocular degeneration who experienced transient visual hallucinations. In a discussion of the case, Newmark (4) raised the possibility of a seizure disorder and suggested further evaluation with an EEG and a computed tomography (CT) scan of the head. Certainly, a convulsive etiology should be considered in the differential diagnosis, and an assessment of this possibility should be made. However, if a seizure focus is not found, the patient should not be treated with anticonvulsants. In the case of Ms. A, neither an EEG nor a CT scan was obtained, as she responded to psychotherapy. It seems that dealing with the ocular pathology and providing psychotherapeutic support is a more appropriate treatment plan.

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Trazodone and Anorgasmia

SIR: Although female anorgasmia caused by monoamine oxidase inhibitors, tricyclic antidepressants, and the benzodiazepine alprazolam has been reported in the literature (1, 2), such a dysfunction associated with trazodone has not been reported, to our knowledge. Trazodone, a triazolopyridine antidepressant, has been associated with increased libido in women (3) and priapism in men. Our MEDLINE search, however, revealed no reports of female anorgasmia associated with trazodone.

Ms. A, a 60-year-old woman, presented with a 20-year-history of dysthymia. She had obtained only partial relief from doxepin, 200 mg/day (which she had taken for the last 10 years), and psychotherapy. Treatment with trazodone was begun; however, Ms. A complained of a new problem, anorgasmia. Her sexual history was obtained, and she was tested with the Derogatis Sexual Functioning Inventory (DSFI) (4), a multidimensional inventory that measures sexual drive, fantasy life, experience, and functioning. These sources showed that Ms. A had adequate sexual information, active desire and fantasy, and no previous anorgasmia. The dose of trazodone was increased from 50 to 100 mg/day, and a week later she showed no reduction in anorgasmia. There was no change in her appetite or weight. Twenty-eight days after she started taking trazodone, the medication was discontinued. Within 4 days the patient became orgasmic.

We suggest that trazodone may cause orgasmic inhibition in women similar to ejaculatory inhibition in men (5), although this problem has not been reported in women. It is therefore important for clinicians to ascertain their patients' sexual functioning, since such side effects may foster noncompliance with the treatment regimen.

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Psychoanalysis and Multiple Personality

SIR: While honoring the case of Anna O. as the dawn of their discipline, most psychoanalysts have attached relatively little significance to her "rather clear case of dual personality" (1), evidently seeing it as merely one symptom of a complicated illness. But since *DSM-III* has recognized multiple personality as a full-fledged disorder (and not just an incidental symptom), we have a coincidence: the very first case in the psychoanalytic literature—whatever other diagnoses might also have applied to it—was a case of multiple per-

sonality disorder. If this disorder is rare, then the coincidence is remarkable.

We could dismiss Anna O.'s multiple personality disorder as only a curious, low-probability event—and it was Breuer's case, anyway, not Freud's—were it not that Freud's own first case, described in the same book (2), appears to have been a case of multiple personality disorder also. Frau Emmy von N. had what Freud termed "hysterical delirium which alternated with normal consciousness" (2). By "hysterical delirium" Freud meant an unconsciously controlled alternate frame of mind, not meaningless confusion. These alternate states, while they could sometimes be mistaken for delirium, at other times were so coherent and normal looking, said Freud, that "it was often only possible *after the event* [italics in the original] to distinguish what had happened in a delirium and what had happened in her normal state" (2). That is, although it was true that the patient's normal conversation could be suddenly interrupted by peculiar behavior and non sequiturs (which would end just as suddenly, allowing the patient to proceed with her normal conversation, unaware of what had happened), it was also true, for example, that when Freud first met the patient and asked her age, her reply that she was "a woman dating from the last century" was spoken in such a serious and sober manner that only after reflection did Freud recognize it as the product of an alternate frame of mind.

Thus, it was misleading of Freud to speak of "delirium" alternating with normal consciousness when he was referring to one or more dissociated mental states, during one of which the patient had conversed with him in the first interview, declaring her sense of being a distinct person. (I consider the patient's subsequent explanation of that declaration to have been a rationalization.)

In sum, I cite the first two cases in the psychoanalytic literature in support of the view expressed in *DSM-III-R* that multiple personality disorder "is not nearly so rare as it has commonly been thought to be" (p. 271).

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Relationship of Plasma Imipramine Levels to CNS Toxicity in Children

SIR: Over the past 7 years, we have conducted two clinical trials of imipramine in prepubertal children with major depression: a fixed-dose study and a placebo-controlled study (1–3). In both studies, plasma levels of imipramine and its major metabolite, desipramine, were monitored. During the course of these studies, three children (all girls) of the 80 children treated developed an imipramine-induced delirium—an overall risk of 3.75% for this adverse effect. The medication was immediately discontinued for all three children, and they had a prompt (less than 1 week) resolution of the delirium.

The three girls had plasma levels of imipramine plus desipramine above 450 ng/ml (mean±SD=578±85 ng/ml). Only one other child (a boy) of the 80 developed a plasma level above 450 ng/ml. He had a combined level of 465 ng/ml, which was the lowest for the four children with high plasma levels. Thus, the risk of imipramine-induced delirium at plasma levels above 450 ng/ml was 75%. In contrast, none of the other 76 children, who had plasma levels below 450 ng/ml, developed this toxicity.

This adverse effect presented as confusion, disorientation, impaired concentration/attention, agitation, episodic rage reactions, social withdrawal, and apparent psychotic symptoms (i.e., hallucinations, delusions, and thought disorder). It developed insidiously over 7–10 days in all three cases and was not associated with more pronounced peripheral anticholinergic side effects (e.g., dry mouth) than in children who did not develop delirium. EEGs revealed the following changes from baseline: excessive intermittent slow waves, slower posterior dominant rhythm, paroxysmal abnormalities (both focal and generalized), and exaggerated response to both photic stimulation and hyperventilation.

In two of the three girls, the imipramine-induced delirium was initially interpreted as a worsening of the underlying major depressive disorder. One of these cases was in the placebo-controlled trial, and the treatment team believed that the worsening was due to placebo treatment. The clinical decision in this case would have been to switch to imipramine. The other case was in the fixed-dose trial, which allowed the treatment team to advance the dose at the end of the fixed-dose phase if they felt that the dose was inadequate. This is what they would have decided. However, the laboratory, which was not blind to the combined plasma levels of imipramine and desipramine, aborted these two erroneous decisions.

This letter is the first report from a prospective study of the risk of developing tricyclic-antidepressant-induced delirium and its association with plasma levels of the antidepressant. This association was first reported in 1982 (4) and has been replicated by several investigators, as outlined in a recent review (5). The data reported here, coupled with our previous findings (1–3), underscore the importance of monitoring plasma levels of imipramine to improve antidepressant efficacy and to avoid toxicity when treating prepubertal children who have major depressive disorder.

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AIDS Controversies in the Mirror of History

SIR: Acquired immune deficiency syndrome (AIDS) is unique in its methods of disabling the body's immune defenses, its terrifying presentations, its extremely high mortality, and so on, but it is not unique in its effects on the human mind and on society as a whole. Some of the most dramatic aspects of AIDS—its evocation of fear, blame, and severe infighting—can best be understood through a comparison with other devastating infections in history.

One is reminded of the controversy over syphilis soon after its spread in Europe. The disease became prominent after the army of Charles VIII besieged Naples in 1494–1495. This army contained French, German, English, Swiss, Hungarian, Polish, and Spanish soldiers. There were also Spanish mercenaries defending Naples. Some of the Spanish soldiers on both sides had been sailors with Columbus and presumably had brought syphilis to Europe from America (1).

Many soldiers from this army developed syphilis and spread it into their countries of origin. Among the besieged inhabitants of Naples it was known as the "French disease" or the "Polish disease." The French called it the "Neapolitan disease" or the "Spanish disease." In England it was the "French pox" (2). In Poland a syphilitic person was, and still is, called *francowaty* (having French tendencies). There is even a historical account which says that syphilis was called the "Scottish evil" in the 1700s in Nova Scotia, where it was attributed to the activity of a Scottish soldier (3). This pattern of naming is not confined to Europe. In Japan, for example, syphilis was known as the "Chinese disease." Syphilis was always blamed on another nationality, preferably the enemy of the moment (4).

A further analogy can be made with the great plague of Athens in 430 B.C., the second year of the Peloponnesian War between Athens and Sparta. Thucydides, the Greek historian, himself a survivor of the great plague, left the following description of the effect of this epidemic on the inhabitants of Athens:

> Men now coolly ventured on what they had formerly done in a corner . . . . So they resolved to spend quickly and enjoy themselves, regarding their lives and riches as alike things of a day . . . . Fear of gods or law of man there was none to restrain them . . . . No one expected to live to be brought to trial for his offenses, but each felt that a far severer sentence had already been passed upon them all and hung over their heads, and before this fell it was only reasonable to enjoy life a little. (5)

We can add modestly to the knowledge about AIDS by remembering that AIDS does not occur in a vacuum but in human society, with its 2500-year-old legacy of describing the psychological effects of severe, devastating epidemics. The fear, blame, infighting, and risk-taking behavior evoked by AIDS can be understood in this context. Such understanding can help correct the irrationality and massive projection in the public health debate on AIDS.

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Clomipramine for Obsessive-Compulsive Symptoms

SIR: In their recent article on the use of fluvoxamine to treat 10 patients with obsessive-compulsive disorder (1), Lawrence H. Price, M.D., and associates noted that the magnitude of improvement in scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was significantly correlated with the final Clinical Global Impression score ($r=0.73$, $p<0.05$) and that baseline Y-BOCS scores were significantly correlated with magnitude of improvement on the Y-BOCS ($r=0.80$, $p<0.01$). The authors said that these correlations suggest that "more severely ill patients might have experienced greater symptom improvement" and that greater baseline severity "did not preclude significant improvement."

Our experience with an open clinical trial of clomipramine in 50 patients with obsessive-compulsive symptoms, 15 of whom had primary diagnoses of obsessive-compulsive disorder (2), supports the findings of Dr. Price and associates. In all of our patients, these symptoms had failed to respond to other psychopharmacologic treatments, including standard antidepressants. Response was based on a global rating scale, and those rated unchanged or slightly improved were considered nonresponders, while those rated moderately improved, much improved, or recovered were considered responders. Four patients who had shown initial improvement had to discontinue the drug because of adverse effects, and they were excluded from the analysis.

Valid prestudy MMPIs had been completed by 17 responders and eight nonresponders. The depression scale score was significantly higher for the responders (mean± SD=92.3±14.97) than for the nonresponders (79.1±11.48) ($t=2.42$, $df=23$, $p<0.05$), and 12 (92%) of the 13 patients with depression T scores above 90 were responders. Scores on both the psychasthenia scale and the hysteria scale also tended to be higher for the responders, although the differences did not reach statistical significance (psychasthenia score for responders=86.3±12.46 and for nonresponders= 75.8±12.30, $t=1.99$, $df=23$, $p<0.11$; hysteria score for responders=75.7±11.55 and for nonresponders=64.5± 14.85, $t=1.71$, $df=23$, $p=0.10$).

Several studies (1–4) have shown that fluoxetine, fluvoxamine, and clomipramine are "antiobsessional." Both the article by Dr. Price and colleagues and our own ratings suggest that patients with particularly severe symptoms may benefit most from these drugs, although the finding may in part represent a regression to the mean.

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Eating Disorders and Obsessive-Compulsive Disorder

SIR: A letter to the Editor from Russell T. Joffe, M.D., and Richard P. Swinson, M.D. (1) reported that 16 patients with obsessive-compulsive disorder, seven of whom were women, had normal scores on the Eating Attitudes Test; the authors concluded that their small study "does not indicate a relationship between disorders of eating and obsessive-compulsive disorder." However, the test only taps current eating attitudes and would miss previous eating problems presently in remission. To detect an association of obsessive-compulsive disorder with past eating disorders, inquiry would have to be made specifically into that possibility.

In fact, at least three studies have found an association between current obsessive-compulsive disorder and past eating disorders. In London, Kasvikis et al. (2) found that 16 (11%) of 151 women with obsessive-compulsive disorder (according to *DSM-III* criteria) had a history of anorexia nervosa, while none of 129 men with obsessive-compulsive disorder and none of 100 agoraphobic patients (83% female) had such a history. At the time of presentation, only two of the 16 women with a history of anorexia nervosa still had anorexic symptoms. In Lyon, Cottraux also found an increased proportion of female patients with obsessive-compulsive disorder who had a history of anorexia nervosa (personal communication, December 1986). In New Haven, Rasmussen found a much higher than chance proportion of patients with obsessive-compulsive disorder who had a history of eating disorders, including anorexia nervosa (paper presented in Jerusalem, March 1987).

In all three series of patients, although a past history of eating disorders was unusually frequent among women with obsessive-compulsive disorder, this association was found in only a minority of cases; most patients with obsessive-compulsive disorder had no such history. Demonstration of the association between the two disorders requires 1) a large sample of female patients with obsessive-compulsive disorder and 2) careful inquiry into a past history of eating disorders.

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Seasonal Depression in Postgraduate Medical Trainees?

SIR: The interesting survey of depression in Canadian residents, interns, and fellows by Kirby Hsu, M.D., and Victor Marshall, Ph.D. (1) omits mention of the important finding reported in 1982 (2) that bright artificial light can relieve winter depression. At the latitude of Ontario, where the survey was conducted, the day's shortness is pronounced, just as it is in the Scandinavian countries, where the bright artificial light treatment has been used the most. It would be interesting to conduct a similar survey of a group of residents, interns, and fellows in Texas, where the days are much longer in winter.

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β Blockers in Neuroleptic-Induced Akathisia

SIR: An article by Bernard Dupuis, M.D., and colleagues (1) represents an important attempt to demonstrate that β blockers are helpful in neuroleptic-induced akathisia through a central β_1 mechanism. The authors reported that of 16 patients, eight were successfully treated with propranolol, and three of the remaining eight patients demonstrated partial response. The authors suggested double-blind controlled studies to confirm their hypothesis.

I would like to draw attention to another report, by Jonathan M. Silver, M.D., and colleagues (2), which showed a threefold and a fivefold increase in the blood levels of thioridazine in two patients after administration of propranolol. From these findings it appears reasonable to speculate that it may not be safe to use propranolol to treat akathisia induced by all neuroleptics and that the relationship between the response to propranolol and the characteristics of the neuroleptic may be a more important factor than has been determined so far. Assessment of patients' blood levels of neuroleptics in studies that attempt to assess the role of β blockers in the treatment of neuroleptic-induced akathisia can possibly provide very useful information.

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SIR: In their article on propranolol, sotalol, and betaxolol in the treatment of neuroleptic-induced akathisia, Dr. Dupuis and colleagues concluded that the critical action of β blockers is central and challenged our hypothesis (1) that the peripheral site of action is a relevant one. Anyone who has treated a patient suffering from akathisia—with the constant foot shuffling, shifting, pacing, and finger movements—will

have little doubt that the body is seriously affected in this syndrome. Furthermore, it seems indisputable that all β blockers have profound effects on peripheral autonomic effector sites, such as heart rate and blood pressure, in normal individuals as well as in those with akathisia. The fact that peripheral agents are helpful for specific symptoms associated with akathisia—for instance, for tremor (2–5)—suggests that these symptoms can be affected peripherally.

We do not, however, dispute a concomitant central site of action. Rather, we wish to emphasize that akathisia may best be understood as a condition that results from the dynamic interaction of CNS dysfunction at the cellular level, visceral autonomic and somatosensory overactivity, and cognitive awareness of the resulting distress. Akathisia cannot be understood if the brain is considered to be detached from the body, nor can it be effectively treated by taking this point of view, as evidenced by the inadequacy of the anticholinergic agents traditionally used for this disorder.

There is no indication in the report by Dr. Dupuis and his colleagues of the effects of sotalol after 2 days, except that it failed to suppress the symptoms of akathisia to the same degree as propranolol. (The data that are presented show the akathisia score only for propranolol.) The absence of data on betaxolol and sotalol compromises our ability to formulate hypotheses around differential response profiles for hydrophilic and lipophilic drugs. A report of the raw data on sotalol would be welcome, so that one could see whether there was, as we would expect, a partial response in specific parameters. Our work further suggests that combining a benzodiazepine with sotalol would probably be as effective, if not more so, than either a centrally acting agent (e.g., propranolol) or a benzodiazepine alone.

We continue to publish our clinical findings that nadolol, a peripheral agent, is effective in treating disorders that appear to be associated with the interaction of bodily distress and cognitive impairment. Currently we are completing a double-blind study of nadolol for the treatment of aggression in chronically hospitalized patients, the results of which we also expect to publish soon.

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Dr. Dupuis and Associates Reply

SIR: We appreciate the interest in our work expressed by Dr. Bansil and Dr. Ratey and associates. We of course agree with the statement by Dr. Ratey and colleagues that all β blockers, both lipophilics (such as propranolol, alprenolol, and metoprolol) and hydrophilics (such as nadolol and sotalol) have profound effects on peripheral adrenoceptors. However, it seems inappropriate to propose that hydrophilic β blockers act exclusively on peripheral sites. If the rate of transfer of hydrophilic β blockers to the brain is markedly slower than that of lipophilic ones, they do enter the CNS (1–3). Therefore, to propose an exclusive or preponderant peripheral mechanism of action, one would have to observe a rapid improvement (e.g., in up to 2 days), since blockade of peripheral adrenoceptors is obtained within minutes after β blockers are administered by the venous route and within hours after they are given orally.

If the full effects are observed after one or more weeks, the drug must have entered the CNS, and a central mechanism cannot be ruled out. We took these data into account when we designed our trial.

Since our study was an open one with a small number of patients, it is not possible to affirm an exclusive central mechanism of action. However, taking into account the lack of effects observed after the patients had been taking sotalol for 4 days (akathisia scores when they were taking sotalol versus those during the washout period were 5/5, 4/4, 4/4, 2/2, 4/4, and 4/4 for patients 3, 8, 9, 12, 14, and 15, respectively), we propose, as did Zubenko et al. (4), that the effect of β blockers in neuroleptic-induced akathisia is at least predominantly related to a central mechanism.

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Pharmacologic Strategies in Schizophrenia

SIR: The study of pharmacologic strategies in schizophrenia by William T. Carpenter, Jr., M.D., and associates (1) offers considerable hope to chronic schizophrenic patients, torn between the pressure from well-meaning people to comply with medication and the desire to "make it on their own," who have the realistic fear of being on medication the rest of their lives. This study showed that intermittent pharmacotherapy targeted at prodromal symptoms can be a viable treatment option for some patients. Several issues, however, need clarification before we equate the targeted approach with the continuous medication approach.

1. It is unclear from the data of Dr. Carpenter and his colleagues whether the continuous medication group and the

targeted medication group were fully comparable at entry into the study. Since prevention of relapse is one reason for continuous medication, it would be informative if the authors told us the number and the length of previous relapses for both groups. Also, one wonders whether the prestudy drug-free period acted as a selection factor. Some patients could not be maintained drug free. Did this lead to more sick patients becoming part of the continous medication group?

2. The two groups received different management, not just different medication approaches, during the entire study. The continuous medication group did not receive psychosocial therapy, while the target medication group did. The additive and interactive benefits of this therapy were available only to the targeted medication group. In addition, patients needing hospitalization were admitted to different hospitals, and the investigators did not control the length of stay or the treatment. These may have influenced the subsequent course of illness.

3. The medication was to be taken orally. Information on compliance was not provided. Noncompliance would more adversely affect the outcome of the continuous medication group than that of the targeted medication group. Depot injections might have controlled for this.

In terms of relapse rate as a measure of outcome, the two techniques do not appear comparable. We concluded from the article that continuous medication therapy is superior in preventing relapse during the first year after an acute episode, and after this period, targeted medication plus psychosocial support works just as well.

The emphasis on continuous medication in the first year and consideration of targeted therapy during the second year is particularly important if targeted therapy is not to die a premature death. In our university hospital clinic, eight patients with a research diagnosis of schizophrenia were selected for this approach on the basis of high global assessment scores and asymptomatic status for at least 4 months within the first year after an episode. Medication was restarted as soon as prodromal signs were clearly evident. All eight patients experienced full relapse and required hospitalization and high doses of medication, with consequent disruption of their rehabilitation. Of a comparable group of 17 continuous medication patients, four relapsed and needed hospitalization in the same period. Although not an acceptable piece of research, this experience warrants caution in starting targeted therapy prematurely. We agree strongly with Dr. Carpenter and associates that there is a need for more research on the markers for selecting patients for the targeted approach.

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SIR: Two pharmacologic strategies, low-dose and intermittent or targeted treatment, are becoming *de rigueur* in research on the maintenance treatment of chronic schizophrenia. The usefulness of the former remains in doubt. For example, the data of Marder et al. (1) on the 2-year survival rates of schizophrenic patients maintained on low- and conventional-dose therapy with fluphenazine decanoate (31% and 64%, respectively) do not justify use of the low-dose strategy for attaining the objectives of reducing adverse effects and improving psychosocial adjustment. To a lesser degree, these data recapitulate the findings of Kane et al. (2), who demonstrated significantly higher relapse rates in their low-dose groups: 56% versus 7%.

However, in their study on pharmacologic strategies in schizophrenia, Dr. Carpenter and associates compared two groups of 21 schizophrenic patients treated over a 2-year period with either a conventional medication regimen or targeted medication plus psychosocial intervention and demonstrated that outcomes were similar in the two groups. Their targeted medication strategy required less than one-third as much neuroleptic in terms of both absolute amount and patient-days on the drug. This result is obviously very encouraging, although the economic aspect must be stressed, since the targeted medication patients participated in more complex, longer psychotherapy sessions (often including families) which occurred at least twice as frequently as those for the conventional medication group. Furthermore, the validity of the outcome results is directly related to Dr. Carpenter and colleagues' level of certainty that the conventional treatment control group took their medications as prescribed. Many patients on oral medication regimens do not.

An alternative strategy to intermittent pharmacotherapy is the routine use of depot injections for chronic schizophrenic patients with all degrees of severity and compliance. Some potential advantages are as follows. 1) Guaranteed knowledge about patient compliance can lead to more timely interventions to avoid relapse. Accurate assessment of compliance is essential when attempting to decrease maintenance doses. Obviously, only depot injections can ensure this. 2) Because face-to-face patient contact is required, depot injections can provide the context for psychosocial treatments and the opportunity for earlier identification and treatment of extrapyramidal effects, e.g., akinesia, akathisia, and tardive dyskinesia. 3) Even when first-pass effects are factored in, with depot injections there is the possibility of a reduction in absolute medication requirements compared with the amounts commonly recommended for oral administration (3), which could conceivably lead to a reduction in the frequency of tardive dyskinesia.

Despite these potential advantages, this mode of administration has simply not caught on in the United States. In Europe and Canada, expenditures for depot neuroleptics constitute more than 29% of the total dollars spent annually on neuroleptics, while this figure is only 5.7% in the United States. At the Philadelphia Veterans Administration outpatient clinic, less than 7% of our schizophrenic patients (approximately 80 of 1,200) receive depot neuroleptics.

In summary, then, implementation of the depot injection strategy for more chronic schizophrenic patients may be an efficient and practical alternative, or at least a prelude, to low-dose or targeted treatment strategies in minimizing the toxic effects of neuroleptics and providing an opportunity to enhance psychosocial functioning. It behooves us to find out why the depot strategy has not been pursued more vigorously.

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Dr. Carpenter and Associates Reply

SIR: Drs. Pandurangi and Pelonero provide thoughtful comments and questions that permit us to clarify several design issues.

1. The targeted and continuous medication groups were similar at entry. Case assignment was made before drug withdrawal on a stratified random basis, ensuring that the two groups would be comparable in age, gender, and prognostic status. The drug-free period was not a screening factor in our design, but it most assuredly would be in clinical practice. Rather than assigning the more medication-dependent subjects to the continuous drug group, we made random treatment assignments for the patients who had not remained drug free for 28 days on either their first or second attempt.

2. At the time this study was initiated, psychiatrists were likely to express concern about the anticipated benefits of the psychosocial treatment component of the targeted approach. Our belief was that psychosocial treatment would be efficacious. The reported study, however, was not designed to test this hypothesis, since the drug condition was not held constant. Rather, we compared two treatment strategies that differed in several crucial components. The feasibility of a targeted drug strategy was supported, and we will soon publish the final results of a lengthy trial which isolates the drug administration strategy for comparison by providing the same psychosocial treatment to both the continuous and the targeted medication groups.

3. It is true that long-acting depot medication would have reduced noncompliance with the treatment program in one group. However, this would have limited generalization of the conclusions to patients willing to receive depot medication and to clinical settings routinely using injectable medication. We preferred to approximate more closely the typical clinic situation, thus generalizing the findings to more patients. Incidentally, compliance with psychosocial treatment is also an issue affecting one group more than the other, and drug compliance is a very real issue in targeted pharmacotherapy. In fact, since medication is used only when it is thought to be critically needed, any noncompliance in the targeted medication group would be expected to have dire consequences. In contrast, varying degrees of noncompliance in the maintenance group are likely to be tolerated before adverse clinical events result. Thus, noncompliance may actually bias results in favor of the maintenance group. Whether drug-free patients with schizophrenia will take drugs in a timely and targeted manner is perhaps the most important issue being addressed in the targeted strategy.

We agree with Drs. Pandurangi and Pelonero that the targeted approach may be more difficult in the months immediately following hospital discharge, and we will be able to report data supporting this proposition in the final analysis of the larger study. Their clinical experience is quite relevant in this regard. Discovering the criteria that select the appropriate patients and the appropriate time for the application of drug reduction strategies will enhance the effectiveness of the approach. Our overall study design called for the inclusion of all patients, in the hope that we could generate empirical criteria. Commonsense clinical criteria have been articulated elsewhere (1). Clinicians can presently consider various approaches to drug reduction, with an eye toward individualizing risk/benefit profiles.

In response to Drs. Ciccone and Ciccone, because of the diversity of symptom manifestations in schizophrenia, any one of several pharmacologic strategies may be preferable in a given treatment situation. Rather than determining which strategy is best under all circumstances, our work with strategies for reduced medication aims at providing the clinician with an extended variety of pharmacologic approaches from which to select. Continuous standard-dose, continuous low-dose, and targeted neuroleptic treatment, with their different risks, benefits, and levels of acceptability, are all viable alternatives that should be considered in treating the individual patient. Use of depot injections sometimes has decided advantages and should certainly be added to this list of alternatives. Several studies have compared oral and long-acting injection strategies (2–4), and we are presently studying the extent to which the depot route of administration can be spaced in time to achieve effective drug reduction (e.g., every 6 weeks versus every 2 weeks). We are less convinced than Drs. Ciccone and Ciccone that depot injections are a general solution to noncompliance, since this type of drug administration only addresses the problem of the passively noncompliant patient.

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Idiopathic Cardiomyopathy and Panic Disorder in Cardiac Transplant Candidates

SIR: Jeffrey P. Kahn, M.D., and associates reported in their article on idiopathic cardiomyopathy and panic disorder (1) that they found a high prevalence of definite (51%) or probable (31%) panic disorder (according to *DSM-III* criteria) in 35 candidates for cardiac transplant who were suffering from idiopathic cardiomyopathy. The prevalence for the same psychiatric disorder was much lower (16%) in heart transplant candidates afflicted with postinfarction cardiac failure, rheumatic heart disease, or congenital heart disease.

These results disagree with data on heart transplant can-

didates that we are gathering. In a research project designed to assess short- and long-term psychosocial adjustment to cardiac transplant, patients are preoperatively screened for psychiatric disturbances, psychological distress, impairment in quality of life, and so forth. The research started 6 months ago, and to date we have examined 16 patients, 10 suffering from idiopathic cardiomyopathy (2) and six from other cardiac disorders (postinfarction cardiac failure, rheumatic heart disease, etc.). The first group contains eight men and two women, with a mean±SD age of 43±12.5 years. The second group is composed of six men, with a mean age of 53.3±4.8 years. Information about current and past psychiatric functioning was obtained with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (3), administered by an expert psychiatrist.

In the group with idiopathic cardiomyopathy, none of the patients satisfied Research Diagnostic Criteria (RDC) for a definite or probable panic disorder; two patients suffered from a major depressive disorder and one from alcoholism. The psychiatric disturbances were present before the onset of the cardiac disorder. In the second group, one patient reported a major depressive disorder and another suffered from panic disorder and minor depression. In this last case the panic disorder was present before the manifestation of the cardiac pathology.

Our results are from a smaller sample than that of Dr. Kahn and his colleagues; on the other hand, diagnoses were made using a reliable semistructured interview. The RDC for definite panic disorder are similar to the criteria of *DSM-III* but are more restrictive. However, we do not think that this could explain the discrepancy between our results and those of Dr. Kahn and associates. In fact, even if we included probable panic disorder, no one in the group with idiopathic cardiomyopathy would receive a diagnosis of panic disorder.

It is our opinion that a major problem in studying panic disorder and idiopathic cardiomyopathy is how to classify "cardiac" symptoms that are particularly numerous in the list of symptoms for the panic disorder diagnosis but that can be caused by a life-threatening situation or by the anxiety linked to a serious medical disorder. It would probably be helpful in clarifying the relationship between panic disorder and idiopathic cardiomyopathy to make a careful assessment of the presence of panic disorder before the manifestation of the cardiac disease.

We are not convinced that the efficacy of alprazolam at doses as low as 0.25 mg t.i.d. represents support for the diagnosis of panic disorder, as reported by Dr. Kahn and colleagues.

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Dr. Kahn Replies

SIR: Dr. Magni and his colleagues report that they have found an absence of panic disorder in cardiac transplant candidates with idiopathic cardiomyopathy, in contrast to our finding of an 82% prevalence of definite or probable panic disorder. Their brief letter does not allow a full consideration of methodological differences. However, it seems likely that there are major differences in interview technique. Proper diagnosis of panic disorder requires substantial specific expertise in eliciting panic symptoms and in differentiating them from cardiovascular symptoms. This is especially true in end-stage cardiomyopathy patients, who tend to expect somatic symptoms and to deny and suppress emotional symptoms. As we reported in our paper, we asked patients about a variety of paroxysmal panic symptoms and then carefully considered whether the elicited symptoms were part of panic attacks. Commonly, patients at first denied any current abrupt anxiety but then recalled pronounced anxiety with earlier panic attacks and subsequent diminished concern. Finally, patients' reluctance to describe psychiatric symptoms would increase if the interview was a psychiatric screen for transplant suitability. Our patients were reassured that this was not the case.

Strict reliance on a structured interview is not sufficient for accurate diagnosis, and the SADS-L is a poor instrument for diagnosis of panic. It requires a positive response to a single initial question about abrupt panic anxiety. A modification of the SADS-L (the SADS-LA) (1) addresses the inadequacy of the SADS-L in this area. For instance, it asks about the abrupt onset of physical symptoms as well. Katon et al. (2) examined the value of adding specific questions about four core somatic symptoms of panic disorder to the Diagnostic Interview Schedule (DIS) and found that this yielded a substantial improvement in diagnostic accuracy.

As we said in our paper, it seemed unlikely that we were misdiagnosing cardiovascular symptoms and the stress of illness as panic disorder, because panic was uncommon in patients with equally severe illness from other cardiac problems. The effectiveness of alprazolam (sometimes at low doses) for what appeared to be panic disorder did further support the diagnosis.

We agree that studies of idiopathic cardiomyopathy in patients previously diagnosed as having panic disorder would be of value. Some of the relevant literature was discussed in our paper. Our more articulate patients reported panic disorder preceding cardiac disease by months or years, and we are presently exploring this area further. In addition, careful clinical studies of panic disorder should be conducted in cardiac transplant candidates by psychiatrists who are blind to the cardiac diagnoses, which should be established independently with equal care.

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Divided Dose for Methadone Maintenance Patients

SIR: In his paper "Inadequate Plasma Concentrations in Some High-Dose Methadone Maintenance Patients" (1), Forest S. Tennant, Jr., M.D., correctly pointed out that some patients have aberrant methadone metabolism. However, simply raising the dose is not the only possible management strategy for such individuals. In a 1978 paper (2), my colleagues and I described two methadone maintenance patients who had precipitous drops in their serum methadone levels 2–6 hours after their doses. Both patients demonstrated dramatic improvement in their clinical course when the methadone was administered on a divided-dose regimen. I would like to suggest that, for patients who prove to be rapid metabolizers, a divided dose may prove to be preferable to a single larger dose.

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Dr. Tennant Replies

SIR: Dr. Walton astutely describes the preferable pharmacologic treatment for rapid metabolizers of methadone. Unfortunately, the use of divided methadone doses may be prohibited by government regulations as well as by poor compliance by the patient.

I and others have successfully used procedures other than raising or splitting the methadone dose for selected patients with aberrant methadone metabolism who continuously use drugs or alcohol. The concomitant administration of one of the α-adrenergic agonists—clonidine, guanabenz acetate, or guanfacine—and methadone may adequately suppress opioid withdrawal symptoms and prevent drug use. Antidepressants have also been shown to reduce drug use in some patients (1). Alcohol abuse can often be controlled by disulfiram, which can be administered simultaneously with methadone (2). A recent report indicates that methadone patients who use cocaine may be successfully treated with amantadine hydrochloride, given in daily doses of 200–400 mg for 2–6 weeks (paper by L. Handelsman et al. presented in Philadelphia, June 1987).

In a pilot study, I found that L-α-acetylmethadol (LAAM) will effectively maintain about 75% of methadone patients who demonstrate inadequate 24-hour plasma concentrations after a 100-mg dose (paper presented in Philadelphia, June 1987). I recommend that physicians who care for methadone patients develop multiple management strategies for patients who continuously abuse drugs or alcohol despite high daily maintenance doses.

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Ascorbic Acid and Dopamine Activity

SIR: Recent clinical studies have suggested that ascorbic acid may augment the therapeutic response of neuroleptic-treated psychotic patients. Thus, A. James Giannini, M.D., and associates reported (1) that the combination of haloperidol with large quantities (1 g) of ascorbic acid may have an antipsychotic role in the emergency treatment of phencyclidine psychosis. In an independent study of schizophrenic patients on a stable neuroleptic regimen, Beauclair et al. (2) found that open trials of up to 8 g/day of ascorbic acid led to symptomatic improvement in 10 of 13 cases. Although no statistical analyses were performed, the authors observed "relatively selective improvement in positive symptoms," which "argues in favor of an antidopaminergic and/or antipsychotic enhancing effect of ascorbic acid."

Excitement about this therapeutic development is tempered by the preliminary nature of the research and incomplete knowledge of ascorbate's mode of action. We propose that the presumed antipsychotic effect of ascorbate is derived from its biochemical role in converting dopamine to norepinephrine.

Basic research reported in the studies we have mentioned suggests that ascorbic acid in large amounts may exert its antipsychotic effect by inhibiting the transmission of signals that originate from dopamine receptor sites. However, another connection between ascorbic acid and dopamine activity—one that has not been previously implicated in the development or continuation of dopamine-mediated psychosis—needs to be considered: the action of ascorbate in converting dopamine into norepinephrine. At present there is a general consensus that ascorbate plays an influential, if not essential, physiological role in only a dozen or so discrete biochemical reactions. Included on this list is one in which ascorbate is thought to be the physiological reductant in the dopamine β-hydroxylase reaction that converts dopamine to norepinephrine (3). Indeed, this reaction is probably the rate-limiting step in the tyrosine-to-norepinephrine pathway. If so, an excessive and clinically deleterious accumulation of dopamine could result from an ascorbic acid deficiency.

Therefore, we are suggesting that in the studies by Dr. Giannini and associates and Beauclair et al., the supplemental ascorbate may have served at least in part to beneficially increase dopamine β-hydroxylase activity. The observation of a primary effect on positive symptoms of psychosis (2), which have been associated with dopamine excess, is consistent with this position. Also pertinent to this hypothesis is earlier work which indicated that chronic psychiatric patients had low levels of ascorbate in their plasma and required high loading doses of ascorbate to excrete normal amounts of it in their urine (4–6). It was unclear whether this presumed deficiency was chiefly a result of poor dietary conditions, which could have been easily corrected by a supplement containing the recommended daily allowance of ascorbic acid (60 mg), or whether, as a consequence of their illness, these patients required more than the recommended daily allowance.

These clinical and biochemical observations provide a ra-

tionale for exploring further the antipsychotic role of ascorbic acid in dopamine-mediated toxic psychoses as well as schizophrenia. Our group is now doing a controlled study of the role of ascorbic acid in treatment of psychotic patients.

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Dr. Giannini Replies

SIR: Dr. Kanofsky and associates propose an intriguing alternative hypothesis to explain the role of ascorbic acid in reducing symptoms of phencyclidine-induced and chronic psychosis. This model for enhanced dopamine β-hydroxylase activity can possibly explain the observed responses in both conditions. Certainly, the work of Beauclair et al. and the model proposed by Dr. Kanofsky and his colleagues tend to support a greater role for ascorbic acid in phencyclidine psychosis than just "ion-trapping." The possible direct action of ascorbic acid and its significant amelioration of symptoms when used alone is consistent with a major dopaminergic role in phencyclidine psychosis (1).

Also, the model would explain quite neatly the emergence of depressive symptoms in phencyclidine withdrawal (2). Indeed, at least two groups (3, 4) have reported significant improvement in depression and postwithdrawal cravings after treatment with the noradrenergic antidepressant desipramine. Perhaps ascorbic acid's future role will not be limited to treating psychosis by decreasing the dopaminergic supply. Perhaps it will also be used in treating postwithdrawal phencyclidine depression (2) and possibly postcocaine states (4) by increasing noradrenergic tone.

If the model of Dr. Kanofsky and associates survives testing, it should become an important tool in understanding phencyclidine-induced psychosis and depression. It may also furnish us with a relatively benign pharmacologic agent for treating psychosis.

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Treatment of Homosexual Patients

SIR: The letter to the Editor from Stanley E. Harris, M.D., and Mark A. Stevens, Ph.D. (1) arguing that homosexuality is not a pathological condition requires a corrective rejoinder. Many believe that the American Psychiatric Association's and the American Psychological Association's position to that effect, cited in the letter, represents little more than submission to strident homophile propaganda and hence lacks any semblance of scientific validity. A majority of people, lay and professional, continue to regard "committed" homosexuality as an aberration, Dr. Marmor to the contrary notwithstanding (2–5).

The authors are, of course, correct in their view that sexual orientation per se should not prevent anyone from receiving needed treatment, including therapy directed toward, among other goals, assisting him or her to assume or resume healthy heterosexuality. However, their militant assertion that allowing homosexuality to serve as an exclusion criterion for therapy constitutes "prejudicial negligence and malpractice" injects a litigious issue into the matter of patient selection, thus inviting the courts to intervene once again in professional prerogatives. For that matter, it could be argued that malpractice can be construed in the case of a therapist or analyst who fails to treat a homosexual for his or her homosexuality; no doubt some enterprising lawyer has come up with that as a basis for a cause of civil action.

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Drs. Harris and Stevens Reply

SIR: Dr. Rinsley questions both the scientific validity and the ethical integrity of the position taken in 1973 by APA that homosexuality is not a mental illness. A review of the relevant scientific information would not fit into one issue of the *Journal*, but we will briefly review the process by which APA deleted homosexuality from its list of mental disorders.

In 1972, the Massachusetts District Branch passed a resolution requesting that APA remove homosexuality from *DSM-II*. The resolution proceeded through normal channels to the APA Committee on Nomenclature, where the issue

was studied intensively for nearly a year. Evaluation of information from scientific disciplines including anthropology, sociology, psychology, and biology led to the committee's conclusion that homosexuality is not a mental illness and the recommendation that it be removed from *DSM-II*. The Council on Research and Development and the Reference Committee reviewed and approved the findings and recommendation of the Committee on Nomenclature before they were ratified by the Board of Trustees in December 1973. Opponents called for a referendum of the entire APA membership. In 1974 the majority (N=5,854) of the APA psychiatrists who voted upheld the decision of the Board of Trustees; 3,810 opposed the decision and 367 abstained (1). The scientific validity of this decision has been confirmed in two subsequent revisions of *DSM*.

As Dr. Rinsley states, a majority of people in our culture disapprove of a homosexual life style. Other forms of prejudice, such as racism, sexism, and religious intolerance, abound as well. The APA ethical principles state, "A psychiatrist should not be party to any type of policy that *excludes*, segregates, or demeans the dignity of any patient because of ethnic origin, race, sex, creed, age, socioeconomic status, *or sexual orientation*" [our italics] (2). We reaffirm our position that persons who are otherwise eligible should not be excluded from brief focal psychotherapy solely because they intend to remain homosexual or bisexual. A therapist who is unable to provide appropriate care should refer the patient to someone who can. Stridently homophobic therapists who regard homosexuality as an aberration and persist in exclusionary, unethical practices may indeed be inviting the courts to intervene.

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Antidepressants and Mania

SIR: In a recent review article (1), Thomas A. Wehr, M.D., and Frederick K. Goodwin, M.D., took issue with "investigators known for their work in this area" who challenge assumptions that antidepressants cause mania. Despite noting that there was a lack of good supporting data, the authors concluded that "*on balance*, the available evidence *suggests*" [italics mine] that antidepressants can cause mania, as does the general suspicion that this might be the case (the argument seems to be that there can be no smoke without a fire). Also, this is intuitively plausible, since psychostimulants can cause mania-like symptoms even in normal persons.

Regarding the general suspicion, the authors failed to note that the idea that antidepressants might cause mania appeared only after 1965, with the introduction of the catecholamine hypothesis and the consequent suggestion that because mania was mediated by increased amine levels, increasing amine levels might be expected to induce it (2). As late as 1963 some authorities predicted that all antidepressants would be antimanic, and indeed there are reports of the efficacy of tricyclic antidepressants in mania (3). Since evidence in support of the catecholamine hypothesis remains nonexistent, one must wonder whether the expectations that were derived from it should be as compelling as they were. It seems, however, that these expectations now have greater force than ever and have survived the initial hypothesis—maybe in the mysterious way that grins survive Cheshire cats.

Regarding the intuitive plausibility of the theory that antidepressants can induce mania, it should be noted that antidepressants are not psychostimulants (4); therefore, citing the "mania-like" effects of psychostimulants is misleading. An equally plausible counterintuition would be that all antidepressants should be antimanic, as both lithium and ECT are, and there is no good evidence to refute this possibility. Prien et el. (5) collected the largest body of pertinent good data, but unlike Drs. Wehr and Goodwin, they resisted the temptation to claim that antidepressants induce mania and stated only what the data permitted—that imipramine is not prophylactic against mania. Indeed, all that the presented data truly permit is the statement that imipramine, 75 mg, is not prophylactic against mania. Higher doses might be, just as higher doses of lithium and more ECT are needed in mania than in depression, and higher-than-antidepressant doses of imipramine have been reported to be antimanic (3). Drs. Wehr and Goodwin emphasized what selective data suggest rather than support and neglected what is suggested by tricyclic-withdrawal-induced mania or the apparent induction of mania by pharmacologically heterogeneous agents—diltiazem, L-glutamate, cyclosporine, androgens, propafenone, propranolol, metoclopramide, and metrizamide—as well as lithium, carbamazepine, and cognitive therapy (2, 4).

I believe that these investigators have done us a disservice by arguing that antidepressants can induce mania. As they pointed out in their article, Lewis, Winokur, and Angst challenged this assumption, citing the lack of good supporting evidence and thereby indicating neglected areas of research that might surprise us. In contrast, the review by Drs. Wehr and Goodwin will be cited as "evidence," further filling the atmosphere with smoke and making it more difficult for ethics committees to go against popular assumptions and sanction research on the use of antidepressants in bipolar disorders.

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DAVID HEALY, M.D., M.R.C.PSYCH.
Cambridge, England

Drs. Wehr and Goodwin Reply

SIR: Dr. Healy seems to have misunderstood or misread our review. First, we do not take issue with the challenging of assumptions about antidepressants and mania. We made it clear that evidence in support of antidepressant-induced ma-

nia is meager and flawed. We began our discussion of acute antidepressant treatment of depressed bipolar patients by stating that "to our knowledge there have been no placebo-controlled studies (with adequate numbers of subjects)," and we began our discussion of maintenance treatment of bipolar patients by stating that "to our knowledge there is only one prospective, double-blind study . . . in which there was a separate placebo group."

Second, we do not think that our review can be used to argue against further research on this issue. We concluded by stating that "the capacity of antidepressant medications to precipitate mania or hypomania . . . has not, however, been adequately investigated," and we argued that "what is needed are prospective, placebo-controlled studies that include patients most at risk for these reactions and that also evaluate outcome in unipolar and bipolar patients separately." The very last sentence of our paper is a call for further research.

Our review also described major flaws in all of the evidence against antidepressant-induced mania, which had been neglected in previous discussions of this topic and which Dr. Healy ignores completely in his letter. Flawed evidence against a hypothesis can be just as misleading as flawed evidence supporting it.

Dr. Healy presents arguments against the catecholamine hypothesis in order to bolster his case against antidepressant-induced mania, but with respect to our paper, the catecholamine hypothesis is a straw man; we never once mentioned it in our review. In fact, more than 10 years ago we raised serious questions about the catecholamine hypothesis (1). The idea that antidepressants could induce mania did not originate with this hypothesis. As we stated in our review, empirical observations that these drugs might have induced mania-like symptoms in medical patients actually preceded, and led to, their use as antidepressants in the 1950s, 10 years before the catecholamine hypothesis was introduced.

Dr. Healy criticizes our comment that "on balance, the available evidence suggests that some bipolar patients become manic . . . when they are treated with antidepressants." We also stated that "antidepressant medications continue to play a major role in the acute treatment of depression." The practice of medicine is not an academic exercise. The physician must make treatment decisions on the basis of available evidence. In making these decisions, the physician has to consider possibilities suggested by previous experience, even when the best kind of evidence is lacking. We tried to maintain a balanced perspective on the issue, a perspective which is lacking in some other writings on the subject, including Dr. Healy's letter.

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THOMAS A. WEHR, M.D.
FREDERICK K. GOODWIN, M.D.
Bethesda, Md.

Panic and Aggression in Organic Brain Syndrome

SIR: We read with interest the article by Matthew J. Edlund, M.D., et al. (1) on the presence of temporal lobe EEG abnormalities in patients with panic attacks. In all six patients described by the authors, in addition to symptoms of panic the most consistently prominent symptoms were violent and aggressive behaviors. Most of the patients also had identifiable neurological problems that have been reported to be etiologically associated with organic dyscontrol of aggressive behaviors (2): childhood epilepsy (two patients), head trauma, a neurosurgical procedure (leukotomy), and specific temporal lobe abnormalities on the EEG (two patients). We have proposed a diagnostic category called organic aggressive syndrome (3) (similar to organic personality syndrome, explosive type, in *DSM-III-R*) to describe the specific disorder of these patients.

Although carbamazepine has been shown to be effective in some patients, our primary pharmacologic strategy and that of other investigators has been to use β-adrenergic blocking agents to treat patients whose aggressive behavior is likely to be related to CNS disorders (4). In general, benzodiazepines have shown inconsistent results in the treatment of dyscontrol of aggressive behavior; published articles have reported both improvement and exacerbation of violent behaviors (5). Dr. Edlund and associates' report of response of both panic and aggression to a single pharmacologic treatment (carbamazepine or alprazolam) raises the possibility of a biological connection between aggressive behavior and panic symptoms. This finding is consistent with our own clinical experience with brain-injured patients and is further supported by the findings of McGrath et al. (5), who described a patient with panic attacks characterized by anger and rage. We believe that the potential overlap of panic and aggressive symptoms in patients with organic brain syndromes must be further documented by operationalized diagnostic criteria such as those of *DSM-III-R* and rating scales such as the Overt Aggression Scale (6) to elucidate whether, or how commonly, such an association exists. If panic disorder and organic aggressive syndrome are found to coexist in patients with organic brain syndromes, further insights into the etiologies, pathogenesis, and treatment of these disabling symptoms may be discovered.

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STUART C. YUDOFSKY, M.D.
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JONATHAN M. SILVER, M.D.
New York, N.Y.

Dr. Edlund and Colleagues Reply

SIR: We have read the letter from Drs. Yudofsky and Silver with interest. Though the main intent of our report was to

highlight the need for an organic workup in patients with atypical panic symptoms, the points made by Drs. Yudofsky and Silver about studying the causes and treatment of organically derived aggression are well taken. Ever since Paul MacLean's famous work with squirrel monkeys (1), the temporal lobe has been understood to be involved with fight-or-flight responses as well as aggression. Not surprisingly, some of the first clinical reports describing panic attacks considered them probable organic phenomena of temporal lobe origin (2). We feel that the idea of a new diagnostic category for organic aggressive disorders has considerable merit. More important, independent ratings of aggressiveness as a separate clinical dimension should be far more widespread in psychiatric clinical studies.

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MATTHEW J. EDLUND, M.D., M.O.H.
ALAN C. SWANN, M.D.
JEFFREY L. CLOTHIER, M.D.
Houston, Tex.

Mental Illness and Creativity

SIR: In her article "Creativity and Mental Illness: Prevalence Rates in Writers and Their First-Degree Relatives" (1), Nancy C. Andreasen, M.D., Ph.D., reported a high rate of affective disorders among participants at the University of Iowa Writers' Workshop and among their first-degree relatives. She stated that when she began her study, she set out to "test the hypothesis of an association between schizophrenia and creativity, since an association between creativity and affective disorder was not even suspected at that time."

This formerly held hypothesis of an association between schizophrenia and creativity surprised us, and we therefore examined the references Dr. Andreasen cited as we looked for an explanation. Close reading of an article by Karlsson (2) revealed several errors that led him to suggest a "genetic association of giftedness and creativity with schizophrenia." We feel that his data more strongly support a link between creativity and affective disorder.

From three genealogy books, Karlsson obtained the names of 1,959 men born between 1881 and 1910; these became his general population control group. To establish a base rate of "giftedness," he examined the 1944 and 1965 indexes of *Who's Who in Iceland* and found 181, or 9.2%, of the control subjects listed in at least one of the editions. Among the 181 "gifted" were 13 scholars, novelists, poets, painters, composers, and performers whose occupations Karlsson defined as creative.

Karlsson next examined the 1851–1940 records of the Kleppur Mental Hospital for cases with family data that would allow identification of male relatives born between 1881 and 1910. Twenty-eight of 213 first-degree relatives of schizophrenic patients and 16 of 69 first-degree relatives of manic-depressive patients were listed in *Who's Who*. Of 362 first- and second-degree relatives of schizophrenic patients, five were engaged in creative occupations; six of 124 first- and second-degree relatives of manic-depressive patients were noted for creative achievements.

For his analyses, Karlsson combined the data from the schizophrenic and manic-depressive groups, stating that the "major psychoses are closely related genetically." Our reevaluation showed that the rate of appearance in *Who's Who* by gifted relatives of schizophrenic patients was significantly greater ($p=0.033$) than that of relatives of the control population, but the association between giftedness and affective disorder was much stronger ($p=0.0001$). The rate of creativity among relatives of schizophrenic patients was not significantly high ($p=0.11$), but the relatives of the patients with affective disorders were noted for creative achievements at a much higher rate than the relatives of control subjects ($p<0.0001$).

Karlsson did not state what criteria were used for assigning diagnoses to the index patients. We think that some patients diagnosed as schizophrenic might, by *DSM-III-R* criteria, be reclassified as having affective disorders. The impact that diagnostic reclassification might have on associations between creativity and giftedness is not discernible from Karlsson's presentation. We suspect, however, that rediagnosis would preserve our finding that Karlsson's earlier work, which he thought showed an association between schizophrenia and creativity, in fact supports an association of giftedness and creativity with affective disorder.

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MARK S. GEORGE, M.D.
J. ALLEN MELVIN, M.D.
DOUGLAS MOSSMAN, M.D.
Charleston, S.C.

Dr. Andreasen Replies

SIR: I agree with all the points made by Dr. George and associates. Karlsson's working hypothesis that creativity was associated with schizophrenia appears to have prevented him from seeing the actual association with affective illness that was implied in his data—another instance of Popper's wisdom in urging us to set a fundamental scientific goal of seeking to disconfirm our hypotheses.

NANCY C. ANDREASEN, M.D., PH.D.
Iowa City, Iowa

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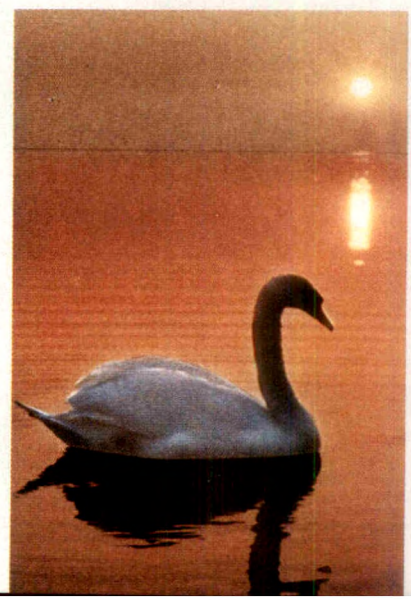
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Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General****—Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (i.e., represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-marketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

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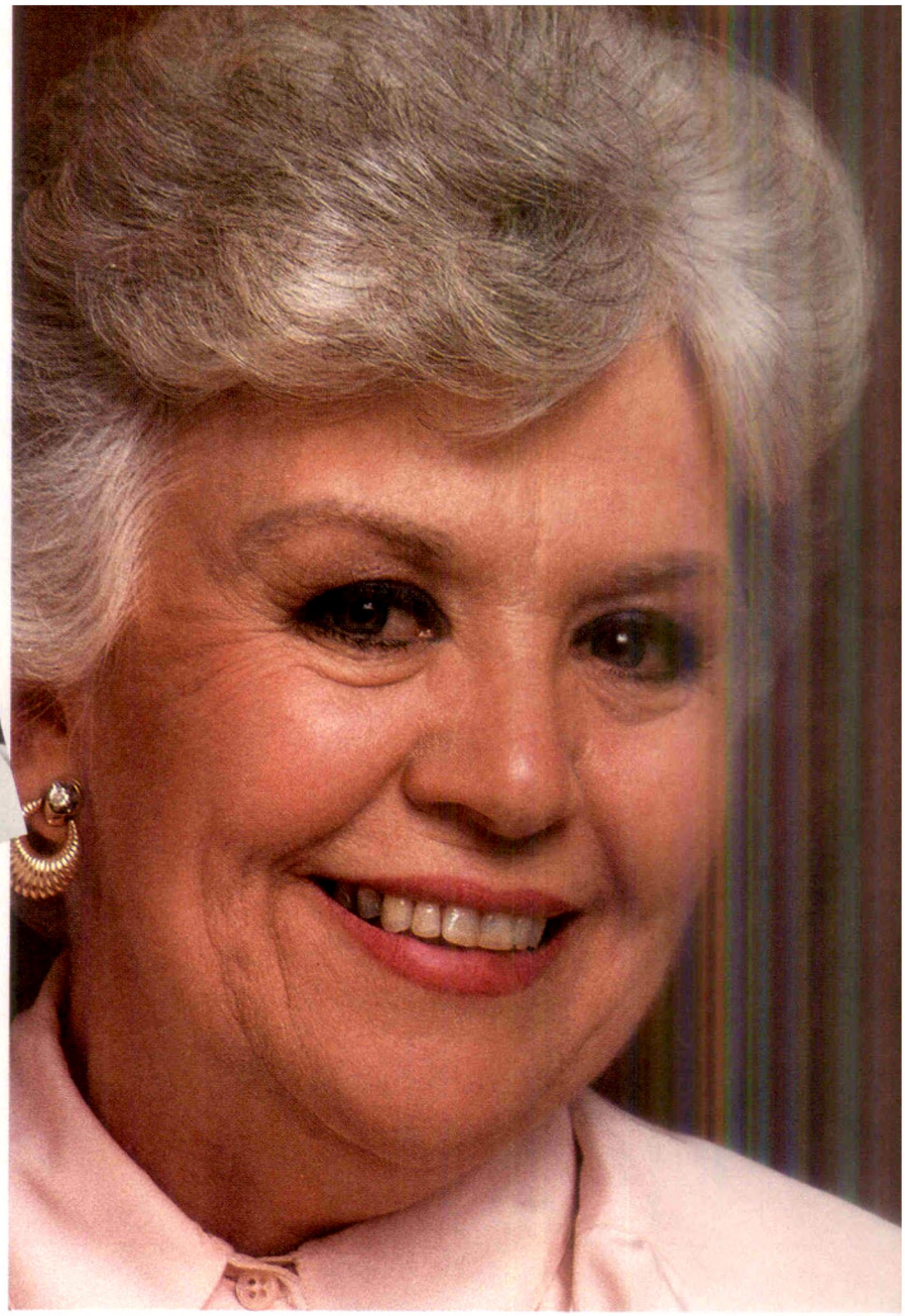
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A benzodiazepine withdrawal syndrome...



It doesn't have to be the price of efficacy.

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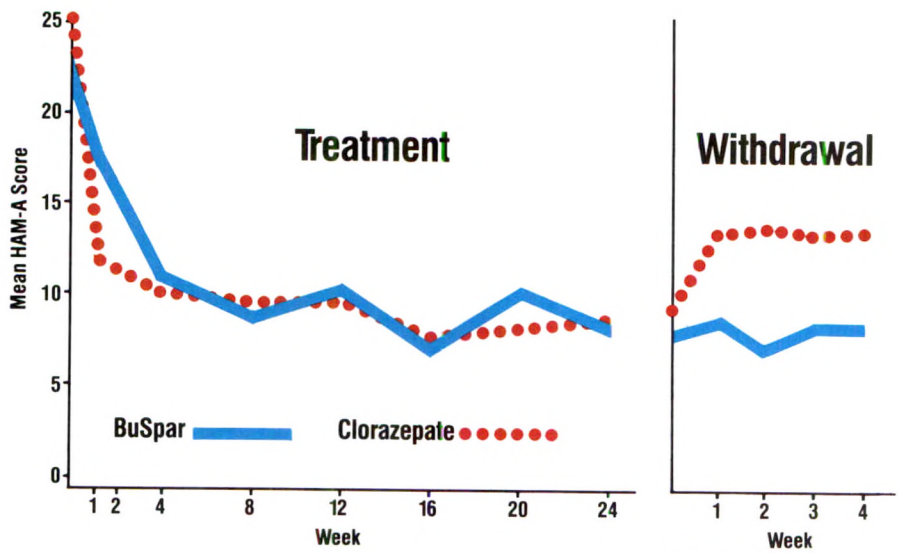
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The anxiolytic that breaks the link between efficacy and a withdrawal syndrome

Proven anxiolytic efficacy during treatment... without a withdrawal syndrome when therapy ends[1]

During therapy, BuSpar-treated patients and clorazepate-treated patients experienced significant reductions in Hamilton Anxiety Scale scores. Upon discontinuation of therapy, however, clorazepate-treated patients experienced a significant increase in HAM-A Scale scores, indicating the emergence of a withdrawal syndrome —BuSpar-treated patients did not.



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Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. **All** significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3, 17$, $p<0.05$)." Reviewers will evaluate the appropriateness of the analyses.

Abbreviations. Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

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1. Glick ID, Hargreaves WA, Drues J, et al: Short versus long hospitalization, a prospective controlled study, VII: two year follow-up results for nonschizophrenics. Arch Gen Psychiatry 1977; 34:314–320
2. McNamara JR (ed): Behavioral Approaches to Medicine. New York, Plenum Press, 1979
3. Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in Endorphins in Mental Health Research. Edited by Usdin E, Bunney WE Jr, Kline NS. New York, Oxford University Press, 1979

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Tables

Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

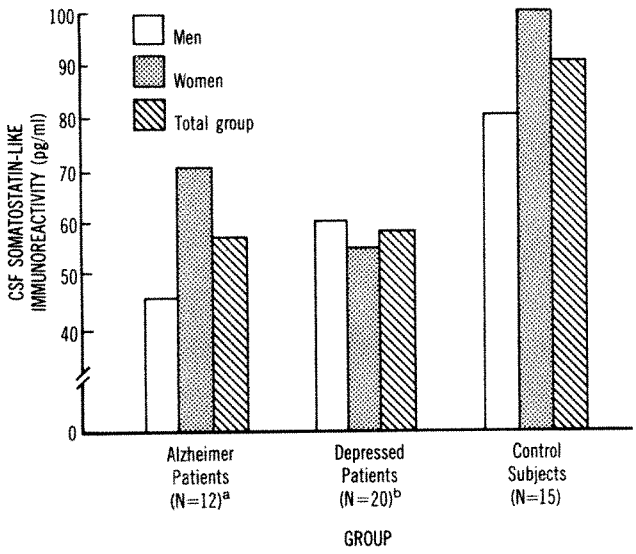
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FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



[a]Significant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).
[b]Significant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

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2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.
3. Error bars should not be used.
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5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.
6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.
7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).
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THE BRITISH JOURNAL OF PSYCHIATRY

MAY 1988 VOLUME 152

Annotation

The benzodiazepine receptor and its role in anxiety. *S.E. File* 599

Review Article

Childhood and adolescent depression: I. Epidemiological and aetiological aspects. *A. Angold* 601

Papers

The assessment of psychophysiological reactivity to the expressed emotion of the relatives of schizophrenic patients. *N. Tarrier, C. Barrowclough, K. Porceddu and S. Watts* 618

Schizophrenic first-rank symptoms in organic mental disorders. *A. Marneros* 625

Marital problems and sexual dysfunction: how are they related? *J. Rust, S. Golombok and J. Collier* 629

Female unemployment and attempted suicide. *K. Hawton, J. Fagg and S. Simkin* 632

Prevalence of transsexualism in the Netherlands. *P.L.E. Eklund, L.J.G. Gooren and P.D. Bezemer* 638

Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. *N.D. Volkow, N. Mullani, K.L. Gould, S. Adler and K. Krajewski* 641

HIV infection associated with symptoms indistinguishable from functional psychosis. *N. Buhrich, D.A. Cooper and E. Freed* 649

The dexamethasone suppression test in bulimia nervosa. *G. O'Brien, F. Hassanyeh, A. Leake, K. Schapira, M. White and I.N. Ferrier* 654

Predicting the response of depressed patients to biological treatment: the dexamethasone suppression test versus clinical judgement. *E.D. Myers* 657

Validity and reliability of the Chinese Hamilton Depression Rating Scale. *Yanping Zheng, Jingping Zhao, M. Phillips, Jianbai Liu, Minfang Cai, Shengqi Sun and Miaofeng Huang* 660

Cyclic AMP second-messenger signal amplification in depression. *R.P. Ebstein, B. Lerer, B. Shapira, Z. Shemesh, D.G. Moscovich and S. Kindler* 665

AIMS ratings—repeatability. *J.A. Bergen, N.B. Carter, J. Craig, D. MacFarlane, E.F. Smith and P.J.V. Beumont* 670

Dysmorphophobic avoidance from disturbed bodily perception: a pilot study of exposure therapy. *I. Marks and J. Mishan* 674

Visually evoked potentials in elderly patients with primary or multi-infarct dementia. *C.E. Wright and P.L. Furlong* 679

Behavioural disorder in the mentally handicapped: the role of life events. *M. Ghaziuddin* 683

Hysterical behaviour in patriarchal communities: four cases, one with Ganser-like symptoms. *M.P.I. Weller* 687

Point of View

Evaluation of treatment effectiveness in psychiatric research. *R.G. Newcombe* 696

Brief Reports

Patterns of psychiatric morbidity in a genito-urinary clinic: a validation of the Hospital Anxiety Depression scale (HAD). *P. Barczak, N. Kane, S. Andrews, A.M. Congdon, J.C. Clay and T. Betts* 698

Schizophreniform psychosis associated with the menstrual cycle. *C. Gerada and A. Reveley* 700

A case of a delusional psychotic syndrome in the setting of Werner's syndrome (adult progeria). *T.C.A. Tannock and R.E. Cook* 703

The mortality of long-stay patients following interhospital relocation. *R.K. Morriss, P.C.W. Bowie and P.V. Spencer* 705

Parasuicide and appendicectomy. *C.A. Vassilas* 706

Subacute sclerosing panencephalitis (SSPE) presenting at the age of 21 as a schizophrenia-like state with bizarre dysmorphophobic features. *E.A. Salib* 709

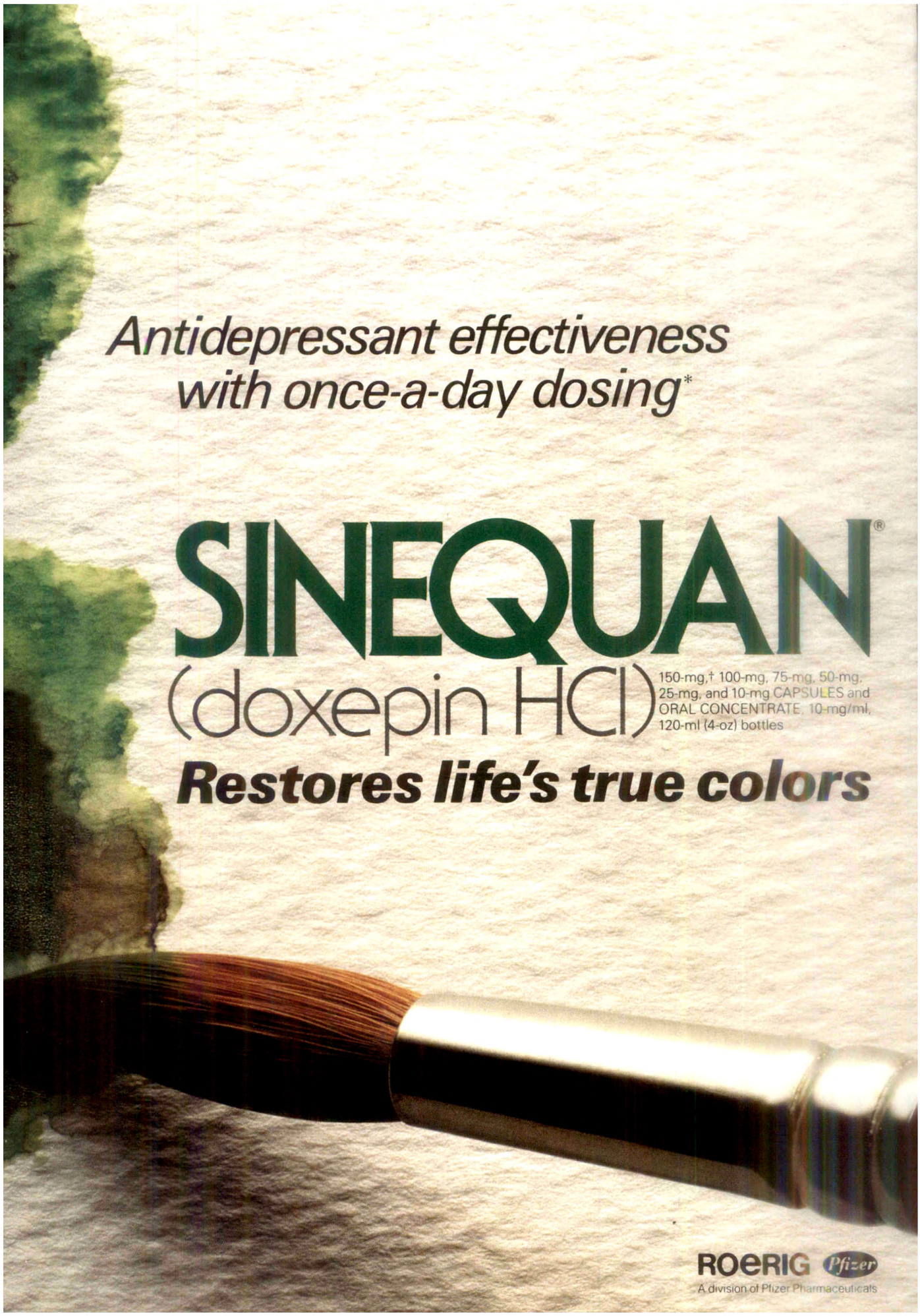


*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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Antidepressant effectiveness
with once-a-day dosing*
SINEQUAN®
(doxepin HCl)
150-mg,† 100-mg, 75-mg, 50-mg, 25-mg, and 10-mg CAPSULES and ORAL CONCENTRATE, 10-mg/ml, 120-ml (4-oz) bottles
Restores life's true colors
ROERIG
Pfizer
A division of Pfizer Pharmaceuticals

SINEQUAN® (doxepin HCl)

BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate
Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.
A. Signs and Symptoms
1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.
B. Management and Treatment
1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 145, Number 8 August 1988

In this issue:

Conceptual and Methodological Issues in Comparative Studies of Psychotherapy and Pharmacotherapy, I: Active Ingredients and Mechanisms of Change

By Irene Elkin, Paul A. Pilkonis, John P. Docherty, et al.

Psychiatric Decision Making in the Emergency Room: A Research Overview

By Daniel C. Marson, Mark P. McGovern, and Hyman C. Pomp

The Heterogeneity of Schizoaffective Disorder: Implications for Treatment

By James J. Levitt and Ming T. Tsuang

Official Journal of the American Psychiatric Association

Physicians prescribe Ativan for what it doesn't do—as well as for what it does



Only Ativan offers all these benefits...

rapid relief of anxiety

clearance not significantly delayed by age, liver or kidney dysfunction

cumulative sedative effects seldom a problem (Sedation, reported in 15.9% of patients in clinical trials, was generally mild and transitory.)

little likelihood of drug interaction (All benzodiazepines produce additive sedative effects when taken with alcohol or other CNS depressants.)

no significant changes in vital signs in cardiovascular patients*

short duration of action, simple metabolism

*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

Ativan®
(lorazepam) IV

Specify Ativan—and assure your patients' therapy

Indicate one of the following on your prescriptions, as appropriate to your state laws:

- Do not substitute
- Dispense as written
- Medically necessary
- Brand necessary
- May not substitute
- No substitution
- NDPS (no drug product selection)

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief o symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety o tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assesse by systematic clinical studies. Reassess periodically usefulness of the drug for th individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angl glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg t avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or car diovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when trea ment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic bloo counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturat or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potentia emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotate limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fet resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matte of urgency, use of lorazepam during this period should almost always be avoide Possibility that a woman of child-bearing potential may be pregnant at institution therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association wi the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multip agents may have been taken. Manifestations of overdosage include somnolence confusion and coma. Induce vomiting and/or undertake gastric lavage followed general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.



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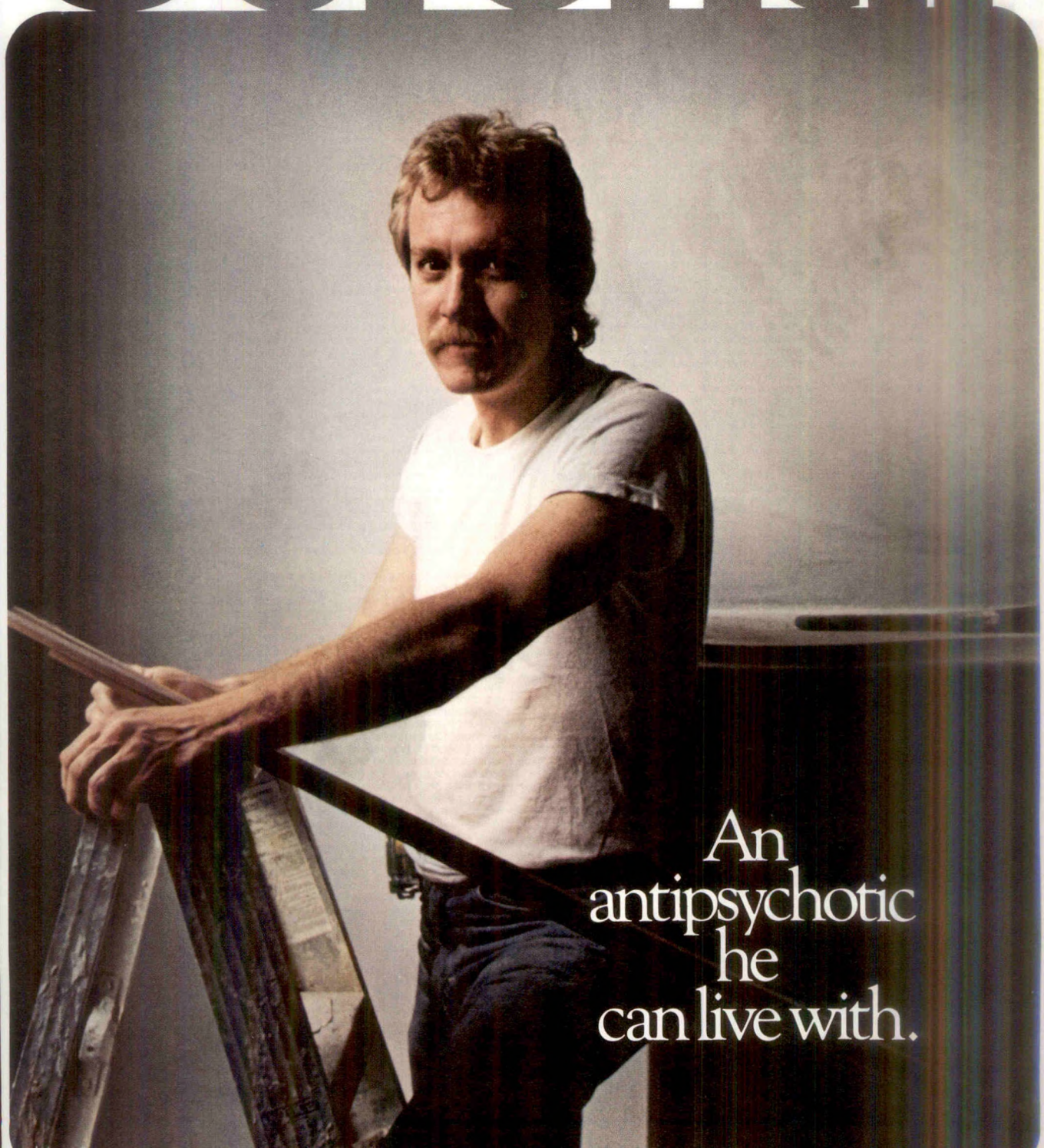
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Treatment Decisions Hospitalization

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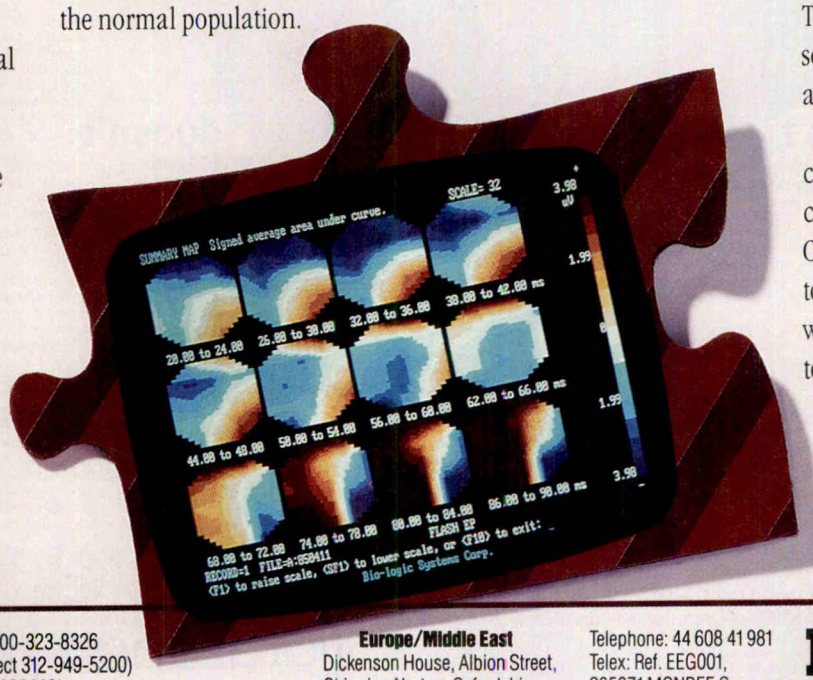
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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 145, Number 8 August 1988

SPECIAL ARTICLES

909 Conceptual and Methodological Issues in Comparative Studies of Psychotherapy and Pharmacotherapy, I: Active Ingredients and Mechanisms of Change *Irene Elkin, Paul A. Pilkonis, John P. Docherty, and Stuart M. Sotsky*

918 Psychiatric Decision Making in the Emergency Room: A Research Overview *Daniel C. Marson, Mark P. McGovern, and Hyman C. Pomp*

926 The Heterogeneity of Schizoaffective Disorder: Implications for Treatment *James J. Levitt and Ming T. Tsuang*

REGULAR ARTICLES

937 PET Imaging of Cortical S_2 Serotonin Receptors After Stroke: Lateralized Changes and Relationship to Depression *Helen S. Mayberg, Robert G. Robinson, Dean F. Wong, Rajesh Parikh, Paula Bolduc, Sergio E. Starkstein, Thomas Price, Robert F. Dannals, Jonathan M. Links, Alan A. Wilson, Hayden T. Ravert, and Henry N. Wagner, Jr.*

944 Patterns of Thought Disorder Associated With Right Cortical Damage, Schizophrenia, and Mania *Ellen Kestnbaum Daniels, Martha E. Shenton, Philip S. Holzman, Larry I. Benowitz, Michael Coleman, Smadar Levin, and David Levine*

950 Somatization and Depression in Fibromyalgia Syndrome *Laurence J. Kirmayer, James M. Robbins, and Morton A. Kapusta*

955 A New Scale for the Assessment of Depressed Mood in Demented Patients *Trey Sunderland, Ina S. Alterman, Donna Yount, James L. Hill, Pierre N. Tariot, Paul A. Newhouse, Edward A. Mueller, Alan M. Mellow, and Robert M. Cohen*

960 Anxiety Disorders in Mid-Adolescence: A Community Sample *Javad H. Kashani and Helen Orvaschel*

965 Predictors of Violence in Civilly Committed Acute Psychiatric Patients *Dale E. McNiel, Renée L. Binder, and Thomas K. Greenfield*

971 Epidemiologic Evidence for Early Onset of Mental Disorders and Higher Risk of Drug Abuse in Young Adults *Kimberly A. Christie, Jack D. Burke, Jr., Darrel A. Regier, Donald S. Rae, Jeffrey H. Boyd, and Ben Z. Locke*

976 Psychiatric Disorder in a Sample of the General Population With and Without Chronic Medical Conditions *Kenneth B. Wells, Jacqueline M. Golding, and M. Audrey Burnam*

982 Fictional Depiction of Suicide in Television Films and Imitation Effects *Alan L. Berman*

EDITORIAL

987 The *Journal*'s New Program of Statistical Review *John J. Sutko, Lee Gurel, and John C. Nemiah*

BRIEF COMMUNICATIONS

989 Preschool Children's Erroneous Allegations of Sexual Molestation *Alayne Yates and Tim Musty*

993 Efficacy of Anticholinergic Prophylaxis for Neuroleptic-Induced Acute Dystonia *George W. Arana, Donald C. Goff, Ross J. Baldessarini, and George A. Keepers*

997 Imipramine and Social-Vocational Adjustment in Chronic Depression *James H. Kocsis, Allen J. Frances, Carlyle Voss, Barbara J. Mann, J. John Mann, and John Sweeney*

1000 *DSM-III*, Draft *DSM-III-R*, and the Diagnosis and Prevalence of Bulimia in Australia *David I. Ben-Tovim*

1003 Case Review and Quantity of Outpatient Care *Barry Blackwell, Mary Gutmann, and Lily Gutmann*

CLINICAL AND RESEARCH REPORTS

1007 Growth Hormone Response to Edrophonium in Patients With Alzheimer's Disease and Normal Control Subjects *Michael Davidson, Bonnie M. Davis, Leo Bastiaens, Joseph Macaluso, Mohsen Arjomand, Theresa Ryan, and Kenneth L. Davis*

1010 Effect of Sodium Valproate in Three Patients With Organic Brain Syndromes *David Kahn, Ellen Stevenson, and Carolyn J. Douglas*

1012 Occult Thyroid Dysfunction in Patients With Refractory Depression *George R. Gewirtz, Dolores Malaspina, Julie A. Hatterer, Susan Fennessen, Donald Klein, and Jack M. Gorman*

1015 Serotonergic and Noradrenergic Sensitivity in Obsessive-Compulsive Disorder: Behavioral Findings *Eric Hollander, Michael Fay, Barry Cohen, Raphael Campeas, Jack M. Gorman, and Michael R. Liebowitz*

1018 Creatine Kinase Elevation After Neuroleptic Treatment *Chester Pearlman, David Wheadon, and Steven Epstein*

1020 Evidence for Atypical Depression in Parkinson's Disease *Randolph B. Schiffer, Roger Kurlan, Allen Rubin, and Sandra Kiser*

1023 *DSM-III* Axis I Diagnoses of Indian Psychiatric Patients With Somatic Symptoms *Shekhar Saxena, Mahendra K. Nepal, and Devinder Mohan*

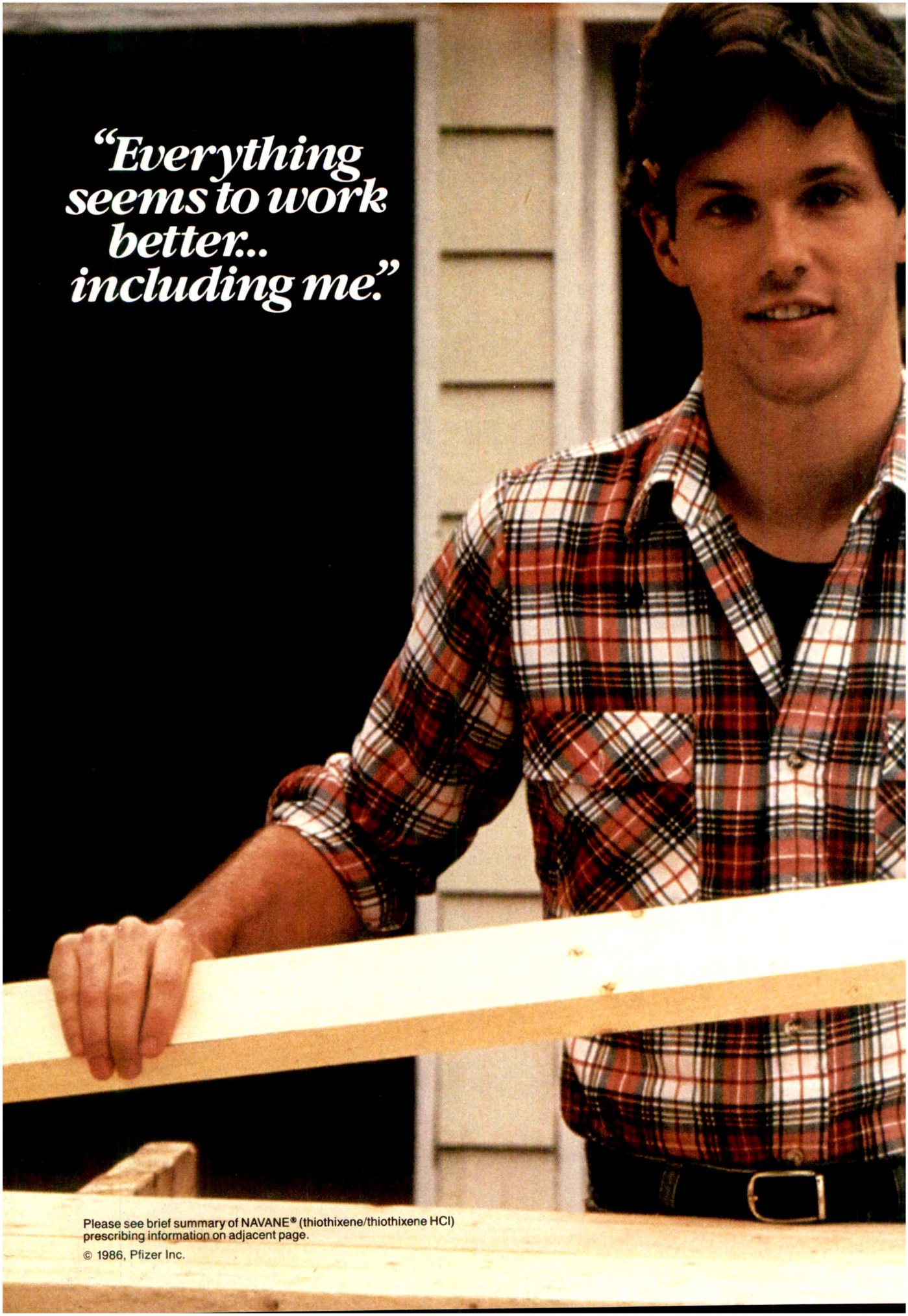
BOOK FORUM 1025

LETTERS TO THE EDITOR 1034

OFFICIAL ACTIONS 1051 1987–1988 Annual Report of the American Board of Psychiatry and Neurology, Inc.

OTHER

A17 Officers of the American Psychiatric Association
A21 Calendar
A47 Books Received
A50 Index to Advertisers



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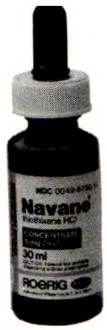
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Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.
Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.
Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.
Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.
Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

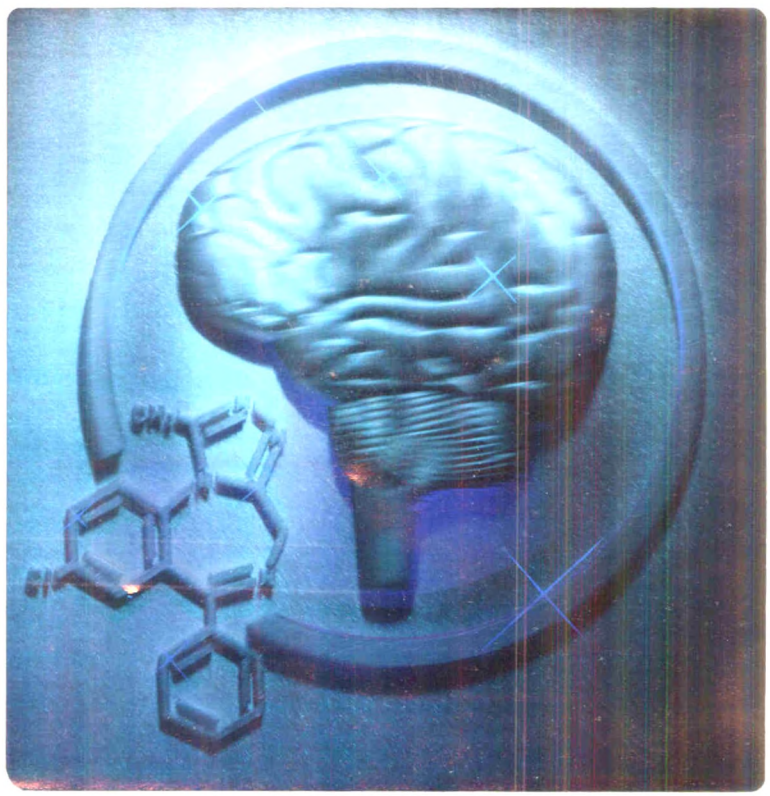
Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.
Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.
Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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XANAX ADDS A UNIQUE DIMENSION TO YOUR PATIENT MANAGEMENT.



FOR ANXIETY ASSOCIATED WITH DEPRESSION.

Xanax® 0.5 mg Tablets

alprazolam

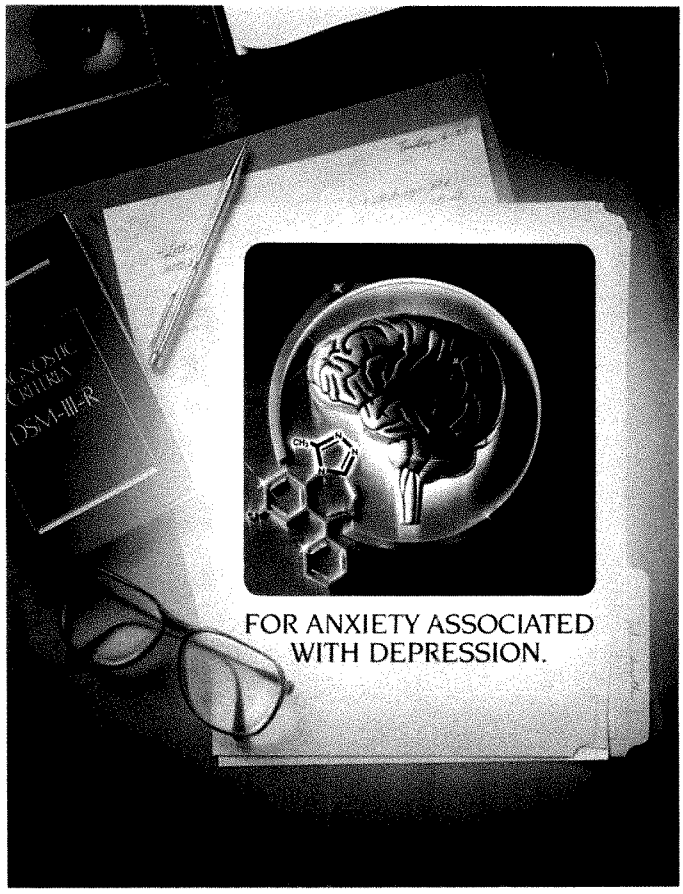
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XANAX ADDS A UNIQUE DIMENSION TO YOUR PATIENT MANAGEMENT.



XANAX® Tablets
(alprazolam, C)

INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women; hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation; thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration).

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose (See Dosage and Administration). Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea, vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitation and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings).

The following adverse events have been reported with benzodiazepine: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

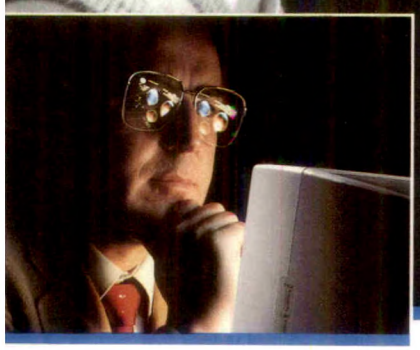
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B-7-
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Xanax® 0.5 mg Tablets
alprazolam C IV

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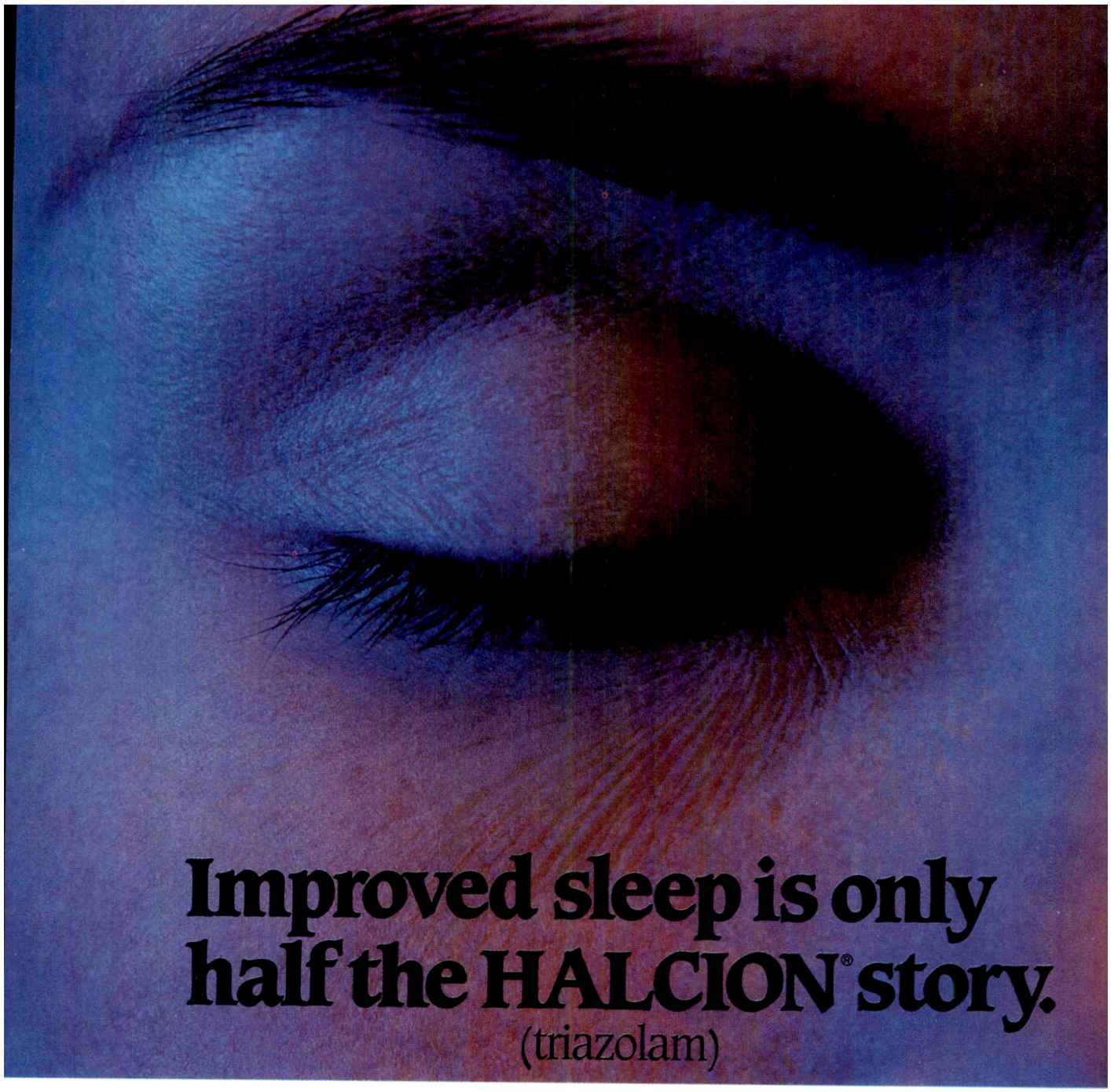
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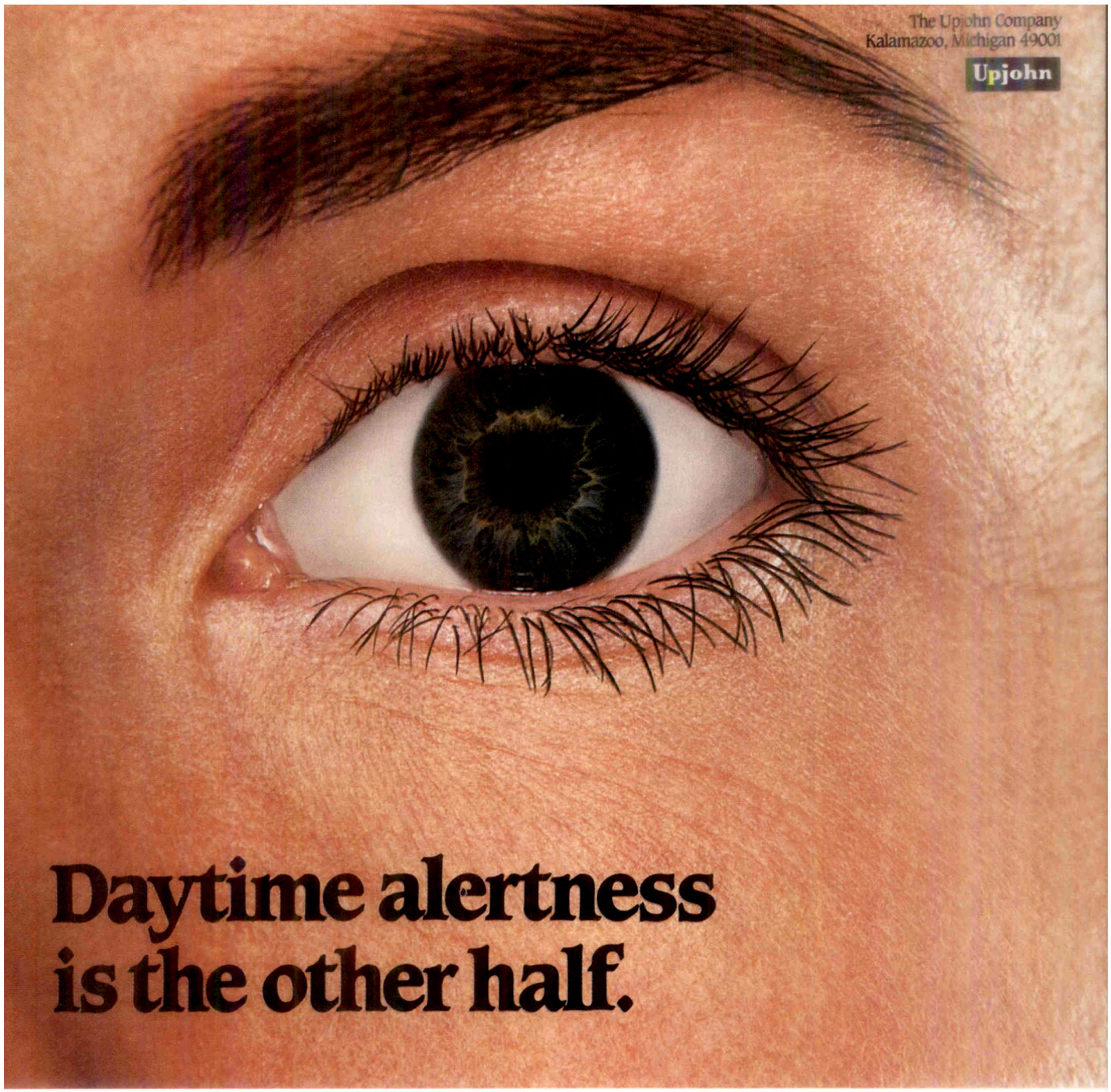
(triazolam)

In depressed patients HALCION is effective when adjunctive insomnia therapy is required.

Disturbed sleep is not an uncommon problem in depressed patients, and although standard tricyclic antidepressants (TCAs) usually relieve insomnia, some depressed patients continue to experience its symptoms. The short-term use of HALCION to relieve insomnia refractory to treatment with TCAs has proven successful in two clinical evaluations.

Effective, concomitant therapy.

HALCION was compared with placebo in a double-blind comparative study of 53 depressed outpatients who had been stabilized on a TCA for at least six weeks but who still suffered refractory insomnia. HALCION was shown to be more effective in relieving the symptoms of insomnia without making depressive symptoms worse.[1]



In another double-blind study comparing HALCION with placebo in 78 depressed outpatients receiving 50-300 mg of imipramine per day, HALCION was significantly more effective in improving most sleep parameters. In addition, there was no evidence that HALCION interfered with the efficacy of imipramine or aggravated the patients' depressive symptoms.[2]

These studies suggest that HALCION is effective adjunctive therapy for the relief of short-term insomnia in depressed patients.

Intentional overdosage of psychotropic medication is more common in depressed patients. Therefore, the least amount of medication that is feasible should be available at any one time.

The recommended dose for most adults is 0.25 mg before retiring. In geriatric and/or debilitated patients, therapy should be initiated at 0.125 mg.

0.125 & 0.25 MG TABLETS

Halcion®

triazolam IV

Helps meet both goals of insomnia therapy

Please see adjacent page for prescribing information.

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HALCION Tablets (triazolam) ®

INDICATIONS AND USAGE: HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS: Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: *General:* In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Some side effects, including drowsiness, dizziness, lightheadedness, and amnesia, appear to be dose related.

Some evidence suggests that confusion, bizzare or abnormal behavior, agitation, and hallucinations may also be dose related, but this evidence is inconclusive. It is recommended that therapy be initiated at the lowest effective dose. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin approximately doubled the elimination half-life and plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. *Nursing Mothers:* Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of HALCION and other benzodiazepines: Amnestic symptoms, confusional states, dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Other events reported include: Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, aggressiveness, falling, somnambulism, inappropriate behavior, and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription. B-5-S

References:

1. Cohn JB: Triazolam treatment of insomnia in depressed patients taking tricyclics. *J Clin Psychiatry* 1983;44(11):401-406.
2. Dominguez RA, Jacobson AF, Goldstein BJ, et al: Comparison of triazolam and placebo in the treatment of insomnia in depressed patients. *Curr Ther Res* 1984;36(5):856-865.

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June 1988

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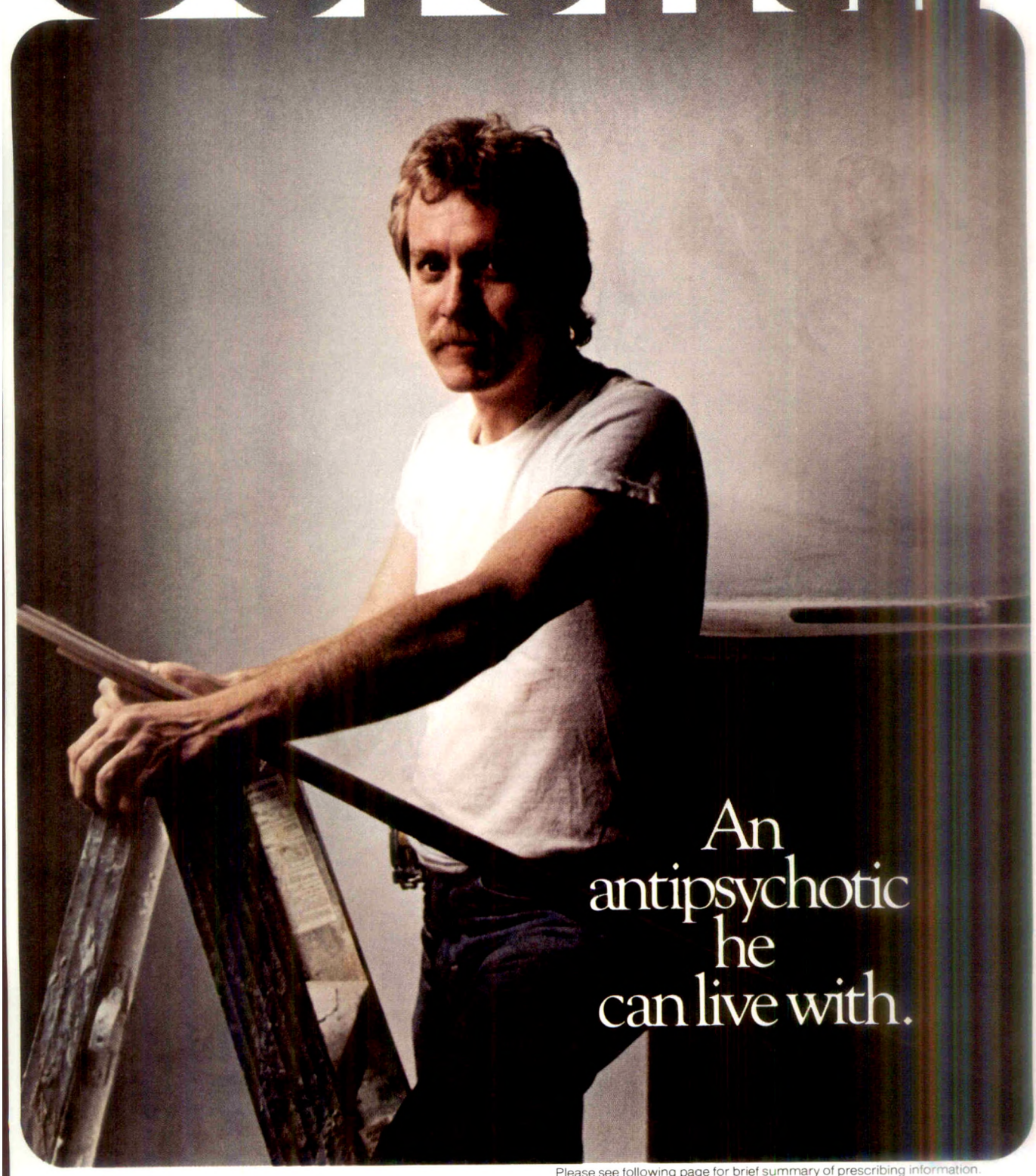
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(mesoridazine) Serentil®

as the besylate
IM/CONCENTRATE/TABLETS



Please see following page for brief summary of prescribing information.

(mesoridazine) as the besylate

Serentil®

(mesoridazine) besylate tablets USP
(mesoridazine) besylate injection USP
(mesoridazine) besylate oral solution USP


Tablets: 10, 25, 50 and 100 mg


Concentrate: 25 mg/ml


Injectable: 1 ml (25 mg)

Brief Summary of Prescribing Information

Contraindications: As with other phenothiazines, Serentil® (mesoridazine) is contraindicated in severe central nervous system depression or comatose states from any cause. Serentil is contraindicated in individuals who have previously shown hypersensitivity to the drug.

Precautions: While ocular changes have not to date been related to Serentil® (mesoridazine), one should be aware that such changes have been seen with other drugs of this class.

Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Serentil. Since convulsive seizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen while receiving Serentil.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Warnings: *Tardive Dyskinesia*: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness 1) that is known to respond to neuroleptic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the section on Adverse Reactions)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Where patients are participating in activities requiring complete mental alertness (e.g. driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

Usage in Pregnancy: The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

Usage in Children: The use of Serentil (mesoridazine) in children under 12 years of age is not recommended, because safe conditions for its use have not been established.

Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.

Adverse Reactions: Drowsiness and hypotension were the most prevalent side effects encountered. Side effects tended to reach their maximum level of severity early with the exception of a few (rigidity and motoric effects) which occurred later in therapy.

With the exceptions of tremor and rigidity, adverse reactions were generally found among those patients who received relatively high doses early in treatment. Clinical data showed no tendency for the investigators to terminate treatment because of side effects.

Serentil® (mesoridazine) has demonstrated a remarkably low incidence of adverse reactions when compared with other phenothiazine compounds.

Central Nervous System: Drowsiness, Parkinson's syndrome, dizziness, weakness, tremor, restlessness, ataxia, dystonia, rigidity, slurring, akathisia, motoric reactions (opisthotonos) have been reported.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and blurred vision have occurred in some instances.

Genitourinary System: Inhibition of ejaculation, impotence, enuresis, incontinence have been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Cardiovascular System: Hypotension and tachycardia have been reported. EKG changes have occurred in some instances (see Phenothiazine Derivatives: Cardiovascular Effects).

Phenothiazine Derivatives: It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, biliary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram, including prolongation of the Q-T interval, lowering and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving the phenothiazine tranquilizers, including Serentil® (mesoridazine). To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, it should be noted that sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing characteristic electrocardiographic changes while taking the drug. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. Hypotension, rarely resulting in cardiac arrest, has been noted.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the **Warnings** section and below.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g. protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for neuroleptic drugs may mask the signs of the syndrome.

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

How Supplied:

Tablets: 10 mg, 25 mg, 50 mg, and 100 mg mesoridazine (as the besylate). Bottles of 100. Ampuls: 1 ml (25 mg mesoridazine [as the besylate]). Boxes of 20.

Concentrate: Contains 25 mg mesoridazine (as the besylate) per ml, alcohol, USP, 0.61% by volume. Immediate containers: Amber glass bottles of 4 fl oz (118 ml) packaged in cartons of 12 bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg and 50 mg of mesoridazine (as the besylate).

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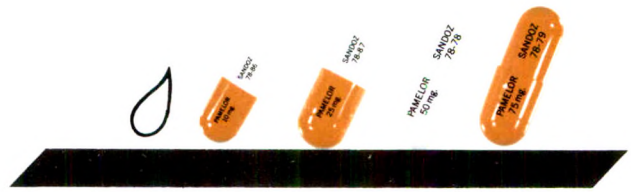
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References: 1. Thompson TL, Thompson WL: Treating depression: Tricyclics, tetracyclics, and other options. *Modern Medicine* 1983;51(8):87-109. 2. Georgotas A: Affective disorders: Pharmacotherapy, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry IV*. Baltimore, Williams & Wilkins, 1985, vol 1, pp 821-833. 3. Roose SP, Glassman AH, Siris SG, et al: Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: A meaningful difference. *J Clin Pharmacol* 1981;1:316-319. 4. Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 413-423. 5. Thayssen P, Bjerre M, Kragh-Sorensen P, et al: Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology* 1981;74:360-364. 6. Ziegler VE, Clayton PJ, Biggs JT: A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry* 1977;34:607-612. 7. Bye C, Clubley M, Peck AW: Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol* 1978;6:155-161.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, par thesias of extremities; incoordination, ataxia, tremors; periphe neuropathy; extrapyramidal symptoms; seizures, alteration in E patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, asso ated sublingual adenitis; blurred vision, disturbance of accommo tion, mydriasis; constipation, paralytic ileus; urinary retenti delayed micturition, dilation of the urinary tract. *Allergic*—Skin ra petechiae, urticaria, itching, photosensitization (avoid excess exposure to sunlight); edema (general or of face and tongue), d fever, cross-sensitivity with other tricyclic drugs. *Hematologic* Bone-marrow depression, including agranulocytosis; eosinophi purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vom ing, anorexia, epigastric distress, diarrhea, peculiar taste, stomati abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in male, breast enlargement and galactorrhea in the female; increasec decreased libido, impotence; testicular swelling; elevation or depr sion of blood sugar levels; syndrome of inappropriate ADH (a diuretic hormone) secretion. *Other*—Jaundice (simulati obstructive), altered liver function; weight gain or loss; perspirati flushing; urinary frequency, nocturia; drowsiness, dizziness, we ness, fatigue; headache; parotid swelling; alopecia. *Withdra Symptoms*—Though these are not indicative of addiction, abr cessation of treatment after prolonged therapy may produce naus headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restle ness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperac reflexes, tachycardia, ECG evidence of impaired conduction, sho congestive heart failure, stupor, coma, and CNS stimulation with c vulsions followed by respiratory depression. Deaths have occur with drugs of this class. No specific antidote is known; general s portive measures are indicated, with gastric lavage. [PAM-Z13—7/5

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OCTOBER

October 3–6, annual meeting, American Academy of Family Physicians, New Orleans. Contact Robert Graham, M.D., Executive Vice-President, 1740 West 92nd St., Kansas City, MO 64114; 816-333-9700.

October 4, annual meeting, Black Psychiatrists of America, Trinidad. Contact Richard A. Fields, M.D., President, P.O. Box 370659, Decatur, GA 30037; 404-243-2110.

October 4–7, Second World Conference on Viruses, Immunity, and Mental Health, Montreal. Contact Prof. Dr. Edouard Kurstak, Dept. of Microbiology and Immunology, Faculty of Medicine, University of Montreal, C.P. 6128, Station A, Montreal, P.Q., Canada H3C 3J7; 514-343-6285; Telex 05267389; Telefax 343-6120.

October 5–8, annual meeting, Southern Psychiatric Association, Colorado Springs, Colo. Contact Margo S. Adams, Executive Secretary, P.O. Box 10002, Tallahassee, FL 32302; 904-222-8404.

October 5–12, annual meeting, International Federation for Medical Psychotherapy, Lausanne, Switzerland. Contact Finn Magnussen, M.D., President, P.O. Box 26, Vinderen, Oslo 3, Norway; 02-146190.

October 6–7, First International Conference on Refractory Depression, Philadelphia. Contact Jay Amsterdam, M.D., Depression Research Unit, Hospital of the University of Pennsylvania, 36th & Spruce Sts., Philadelphia, PA 19104-4283.

October 6–8, annual meeting, National Association for Retarded Citizens, Albuquerque, N.M. Contact Alan Abeson, Ed.D., Executive Director, 2501 Avenue J, Arlington, TX 76006; 817-640-0204.

October 6–9, annual meeting, Canadian Association for Community Living, Regina, Saskatchewan, Canada. Contact Diane Richler, Executive Vice-President, 4700 Keele St., Downsview, Ontario, Canada M3J 1P3; 416-661-9611.

October 6–9, Sixth Biennial International Symposium on Corpus Cavernosum Revascularization and Third Biennial World Meeting on Impotence, Boston. Contact Dept. of CME, Boston University School of Medicine, 80 E. Concord St., Boston, MA 02118; 617-638-4605.

October 7–8, American Medical Association National Conference on Adolescent Mental Health, Oak Brook, Illinois. Contact Desiree Goodwin, 312-645-4526.

October 7–10, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, Boston. Contact John A. Hinckley, Executive Director, P.O. Box 11083, Richmond, VA 23230; 804-355-0147.

October 8–11, Tenth World Congress of the International College of Psychosomatic Medicine, Madrid. Contact Professor J.J. Lopez-Ibor, Clinica Lopez Ibor, Calle Nueva Zelanda 44, Puerta de Hierro, E-28035 Madrid, Spain.

October 9–11, Second Congress, World Association for Psychosocial Rehabilitation, Barcelona, Spain. Contact J.L. Marti-Tusquets, University of Barcelona, Casanova 143, Barcelona 08035, Spain.

October 9–11, national meeting, Mexican Association of Child Psychiatry, Queretaro City, Mexico. Contact Arturo Mendoza, M.D., Vice President, MACP, Patricio Sanz 437, Mexico, D.F. 03100; 905-523-1400.

October 9–15, XIV International Congress of Psychotherapy, Lausanne, Switzerland. Contact President, Prof. M. Burner, Centre Psycho Social, Rue St–Pierre 1, 1003 Lausanne, Switzerland; 021-44-21-33.

October 10–14, Eighth International Forum of Psychoanalysis, Rio de Janiero, Brazil. Contact ADAM Congressos e Eventos Ltda., 63, Av. Almirante Barroso, Grps. 1413–1414, Rio de Janeiro 20031, R.J., Brazil, 021 220-2781 or 021-220-1856.

October 13–15, international conference, The Psychobiology of Human Eating Disorders, The New York Academy of Sciences, New York. Contact Conference Dept., The New York Academy of Sciences, 2 East 63rd St., New York, NY 10021; 212-838-0230.

October 13–15, 9th annual conference, Canadian Group Psychotherapy Association, Toronto. Contact Dr. Kent Mahoney, Holy Cross Hospital, 2210 – 2nd St., West, Calgary, Alberta, Canada T2S 1S6.

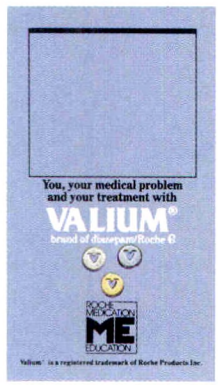
October 13–16, regional symposium, World Psychiatric Association, Washington, D.C. Contact Ms. Ellen Mercer, Di-

(Continued on page A41)

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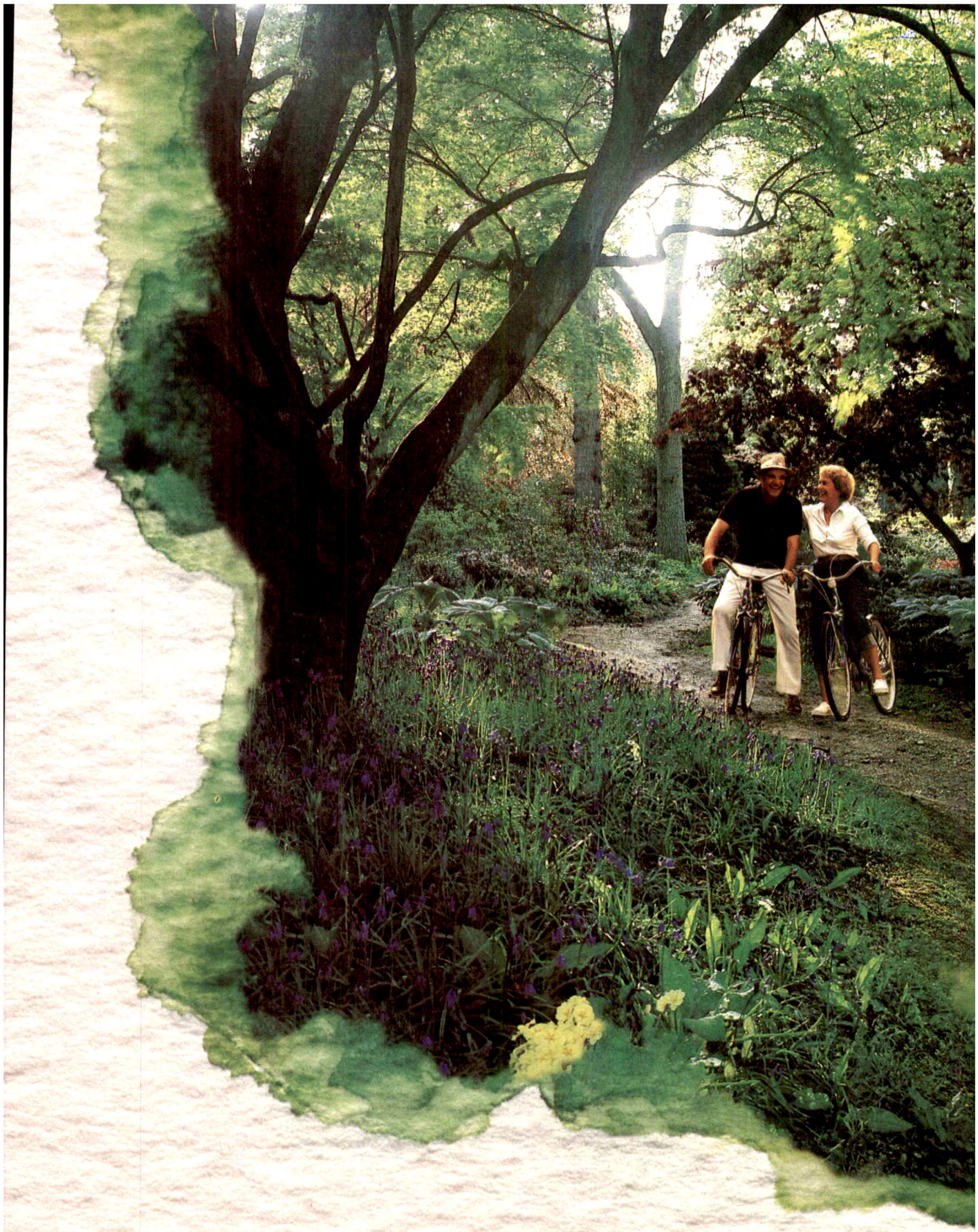
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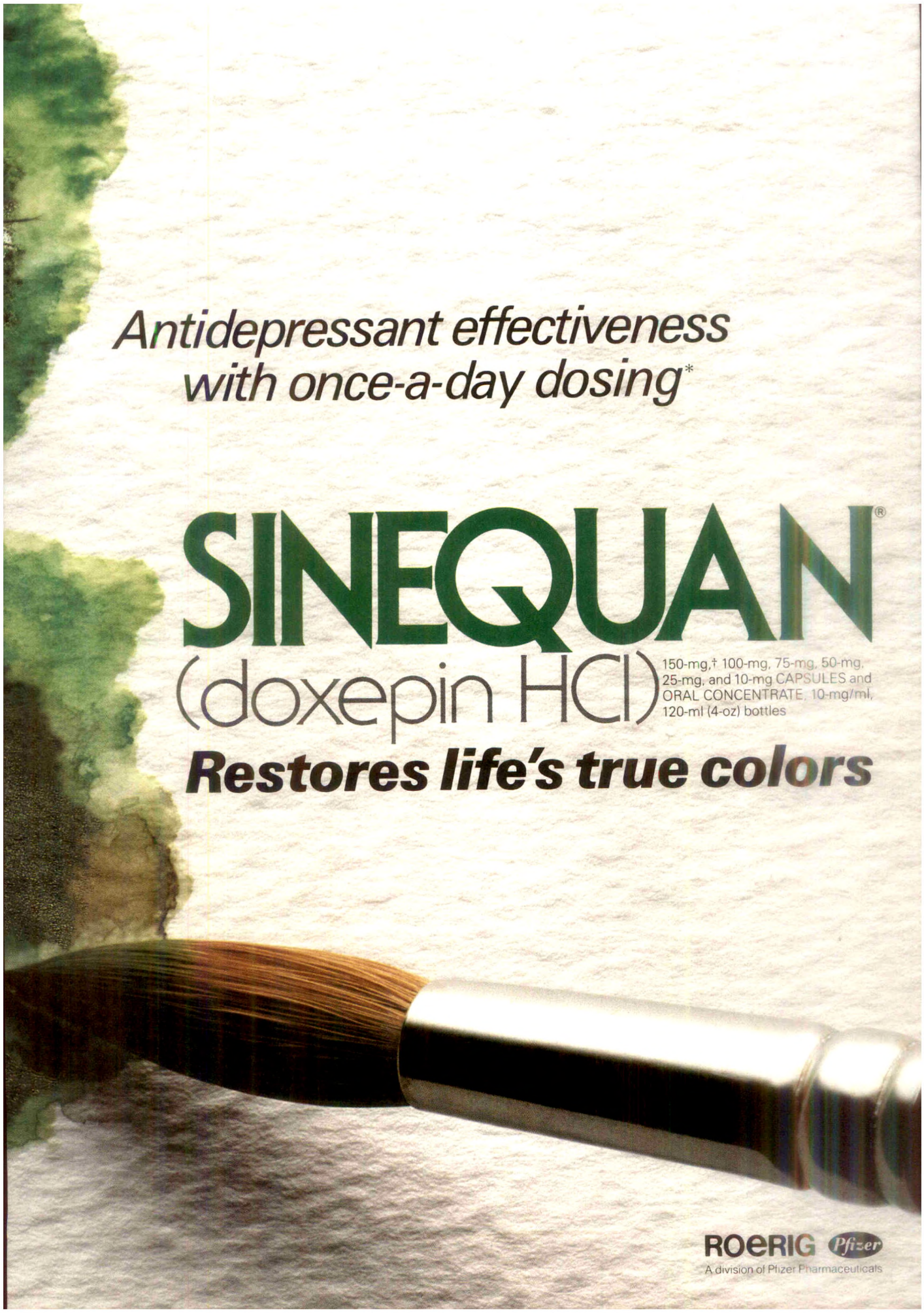


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Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

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MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

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Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

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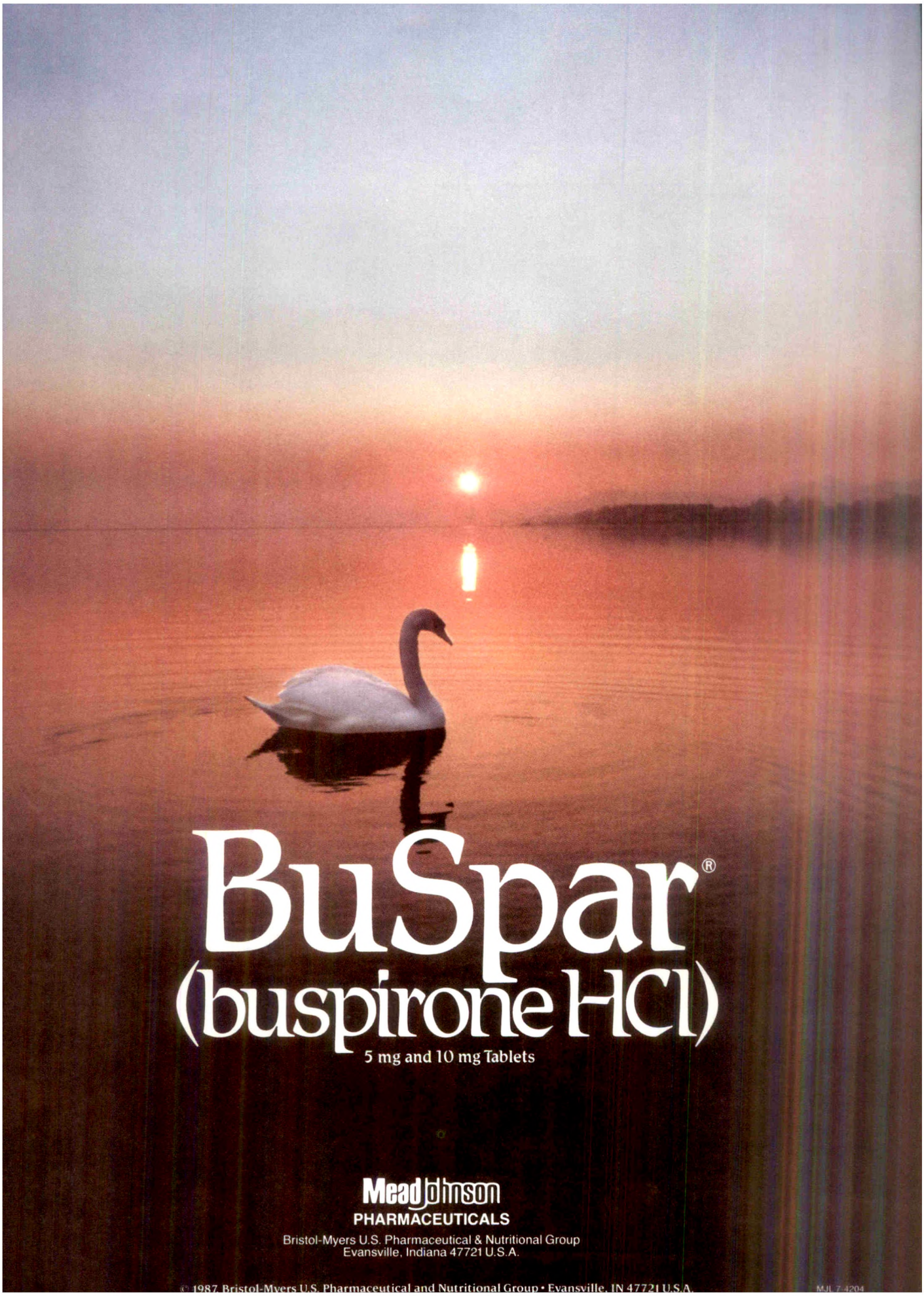
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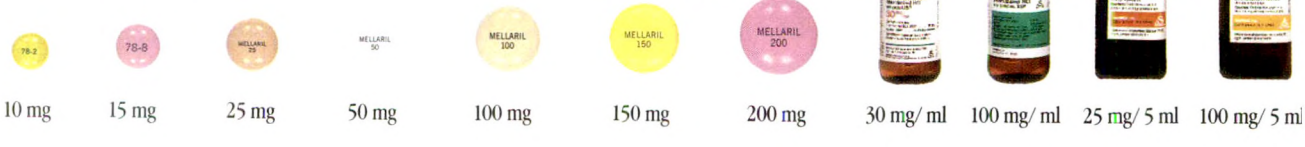
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mood (37). This study also emphasizes that the pathophysiologic response to injury in one hemisphere may be very different from the response to a seemingly similar injury in the opposite hemisphere. PET imaging has demonstrated changes distant from the lesion site and may suggest the involvement of receptor changes in uninjured cortex in the mechanism of poststroke depression.

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Patterns of Thought Disorder Associated With Right Cortical Damage, Schizophrenia, and Mania

Ellen Kestnbaum Daniels, M.Ed., Martha E. Shenton, Ph.D., Philip S. Holzman, Ph.D., Larry I. Benowitz, Ph.D., Michael Coleman, M.A., Smadar Levin, Ph.D., and David Levine, M.D.

The authors used the Thought Disorder Index to measure thought disorder in 23 patients with unilateral right hemisphere cortical damage, 20 patients with bipolar mania, and 25 patients with schizophrenia. There were no differences in the total amount of thought disorder in these groups, but each showed a unique pattern of thought disorder. Patients with right hemisphere damage displayed fragmented thinking, manic patients displayed playful thinking, and schizophrenic patients displayed idiosyncratic thinking. These findings support the view that thought disorder is manifested in different forms that are relatively specific to psychiatric or neurological condition.

(Am J Psychiatry 1988; 145:944–949)

Patients with right hemisphere cortical damage show characteristic problems in the visuospatial realm and also often exhibit psychotic disorders that include hallucinations, confabulations, and incoherent and combinatory thinking (1–7). Although these disorders are similar in some respects to those of functionally psychotic patients, to date there has been no systematic comparison of the patterns of thought disorder displayed by subjects with and without obvious structural brain damage. In the present investigation we will compare the thought disorders of people who have right cerebral hemisphere damage with the thought disorders of manic and schizophrenic patients.

The instrument we used to assess disordered thought in these three groups is the Thought Disorder Index, a well-validated scale developed for studying psychotic patients (8, 9). Through such studies we are attempting to identify both commonalities and distinctive aspects of the thought disorder patterns in different diagnostic groups. Such identifications may also contribute to our understanding of the cognitive consequences of right hemisphere damage.

The appearance of thinking disorders in several pathological conditions poses the question of whether such disorders are uniform across different conditions or whether there are specific qualities of thought disorder that are associated with and perhaps even characteristic of different psychotic conditions. If distinctive types of thought disorder accompany specific pathological conditions, then these thought disorders may be of great use in providing more refined and valid distinctions among these conditions.

Support for the notion that thought disorder is specific to different conditions comes from a recent report by Solovay et al. (10), who, using the Thought Disorder Index, presented evidence that manic thought disorder differs in specifiable ways from schizophrenic thought disorder. Manic thought disorder was distinguished by a noteworthy presence of expansive thinking, loose combinatory activity, and playful, flippant responses. Schizophrenic thought disorder, on the other hand, was characterized by idiosyncratic thinking and fluid ideas, with peculiar, absurd, incoherent, and even neologistic formations. In a second study, Shenton et al. (11) presented evidence that patients with schizoaffective disorder had thought disorders that were typical of both the schizophrenic and manic groups, although the similarity between schizoaffective and schizophrenic patients was more striking.

Unlike patients with damage to the left hemisphere, the linguistic functions of patients with right hemisphere cortical damage are not obviously disrupted, and thus the assessment of thinking pathology is not confounded by basic language and speech disorders (1). Further, the fact that the patients with right hemisphere cortical damage tested for this study had no history of mental disturbance before neurological insult allows one to infer a relation between their impaired organic state and whatever thought disorders they might display.

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METHOD

Subjects

Twenty-three patients with unilateral right hemisphere cortical damage constituted the group of patients with right hemisphere damage. These patients were admitted to a rehabilitation hospital because of sensorimotor deficits and/or confusion following cerebral vascular accident. Patients were included if they met the following criteria: 1) Brain damage was restricted to the right cerebral hemisphere as verified by CT scan and clinical signs such as unilateral (left-sided) sensory and motor deficits and unilateral neglect. 2) The patient was right-handed. 3) The patient's first language was English. 4) The patient had no past history of mental disturbance or psychiatric treatment. The ages of the patients ranged from 35 to 85 years; their mean±SD age was 67.6±14.4 years. Eight male and 15 female patients with right hemisphere damage were tested.

The schizophrenic group consisted of 25 patients with chronic schizophrenia, three women and 22 men. Fifteen were in residence at a state psychiatric facility and 10 resided in a private psychiatric facility. Information obtained from a standardized interview (the Schedule for Affective Disorders and Schizophrenia—Lifetime Version) (SADS-L) (12) was used to make diagnoses of schizophrenia according to Washington University criteria (13), Research Diagnostic Criteria (14), and *DSM-III* criteria. The three sets of criteria were used to ensure that schizophrenic patients (and the manic patients) were prototypic and would be classified similarly by all skilled diagnosticians. The ages of the schizophrenic patients ranged from 18 to 36 years; their mean age was 25.4±4.8 years.

The manic group consisted of 20 patients with bipolar mania, nine women and 11 men, diagnosed according to the aforementioned criteria. Their ages ranged from 16 to 46 years; their mean age was 25.2±9.4 years. The schizophrenic and manic patients had previously been tested in two other studies, and their thought disorder patterns have been described elsewhere (10, 11, 15). As will be described later in this paper, their thought disorder protocols were rescored for this study. To make the protocols of these psychotic patients comparable to those of the patients with right hemisphere cortical damage for the purpose of facilitating blindness in rating, the original 10-card protocols of the schizophrenic and manic patients were reduced to responses to the same four cards to which the patients with right hemisphere cortical damage were required to respond.

There were no significant differences between the groups in socioeconomic status as measured by the Hollingshead Two-Factor Index (16) ($\chi^2=9.1$, df=8, n.s.). There were, however, significant differences among the groups in level of education completed ($\chi^2=9.8$, df=6, $p<0.01$). Manic patients and patients with right hemisphere damage were similar in educational level; schizophrenic patients were less educated. This difference, consistent with demographic characteristics of schizophrenic patients (17), probably reflects the earlier age at onset and poorer premorbid competence of schizophrenic patients compared with manic patients or those with right hemisphere damage.

There were also significant differences in the ages of the three groups ($F=130.5$, df=2, 65, $p<0.0001$). Manic and schizophrenic patients did not differ in age, but both groups were significantly younger than the patients with right hemisphere cortical damage. Since right hemisphere damage generally results from cerebral vascular accident late in life, the only way to match the groups for age would have been either to select unusually young patients with right hemisphere damage or atypically old psychotic patients. We therefore selected prototypic group members; significant age differences among the groups resulted.

Instrument

The Thought Disorder Index (8, 9) was used to assess thinking disorders. This instrument identifies 23 different types of thought disorder at four levels of severity given the weights of 0.25, 0.50, 0.75, and 1.0, yielding both a quantitative and a qualitative assessment of thought disorders. The mildest categories of thought disorder are assigned the weight of 0.25 and the most severe categories receive the weight of 1.0. This index has been shown to record changes in thinking pathology over time reliably and in response to antipsychotic drug treatment (18). Furthermore, differences noted between normal and psychotic groups on this index are not related to gender, ethnicity, social class, or intellectual ability (19). Previous studies (8–10) have established interrater reliability (interclass correlation coefficients) at satisfactory levels: $r=0.87$ to $r=0.93$. The scoring categories and illustrative examples can be found elsewhere (8, 9).

Procedure

After informed consent was obtained from each patient, the Rorschach Test was administered individually in the manner described by Rapaport et al. (20). Patients from the two psychiatric groups were given the full set of 10 cards. Patients with right hemisphere cortical damage were given abbreviated four-card tests due to the difficulty of finding uninterrupted times for testing and the limited attention span of these patients. The subset of cards was chosen to reflect the variety of the 10-card Rorschach Test and consisted of two achromatic cards (IV and VI), one chromatic card (IX), and one red and black card (II). This abbreviated form was compared with the 10-card protocol, and the Pearson correlation between the two sets for total amount of thought disorder was 0.88 (18).

Responses to the same four cards were selected from the protocols of the psychotic patients. In this way the response protocols were made equivalent for

TABLE 1. Thought Disorder Index Factor Scores of Patients With Right Cortical Damage, Schizophrenia, or Mania

Thought Disorder Index Factor	Component Variables	Patients With Right Hemisphere Cortical Damage (N=23) Mean	SD	Patients With Schizophrenia (N=25) Mean	SD	Patients With Mania (N=20) Mean	SD
Combinatory thinking[a]	Flippant thinking, incongruous combinations, playful confabulation	0.60[b]	0.94	0.88[b]	1.67	3.80[c]	2.69
Fragmented thinking[d]	Excessive qualification, concrete thinking, vagueness, fragmentation, confusion	2.65[c]	2.10	0.68[b]	1.22	0.30[b]	0.48
Idiosyncratic verbalization[e]	Peculiar, queer, absurd interpretations, neologisms, incoherence	1.83[b]	1.37	4.16[c]	3.42	1.60[b]	2.06
Associative looseness[f]	Clanging, perseveration, inappropriate distance, loose, fabulized combinations	1.74[c]	2.28	2.56[c]	2.66	4.30[c]	7.62
Arbitrary thinking[g]	Autistic logic, fluid thinking, confusion	0.57[c]	0.90	1.08[c]	1.53	0.65[c]	0.88

[a]One-way ANOVA: F=19.8, df=2, 65, p=0.0001.
[b]Significantly different from scores in same row with superscript c (p≤0.01, Student-Newman-Keuls).
[c]Significantly different from scores in same row with superscript b (p≤0.01, Student-Newman-Keuls).
[d]One-way ANOVA: F=16.9, df=2, 65, p=0.0001.
[e]One-way ANOVA: F=10.3, df=2, 65, p=0.0001.
[f]One-way ANOVA: F=1.27, df=2, 65, n.s.
[g]One-way ANOVA: F=0.81, df=2, 65, n.s.

all groups and blind scoring could therefore be accomplished.

All testing sessions were tape-recorded, and verbatim transcripts of each session were provided by a transcriber. Transcripts were checked for accuracy by the examiner, after which all identifying information was removed. The four-card protocols from all patients from all three groups were then scored for thought disorder in conformity with the Thought Disorder Index scoring manual (8, 9). Three raters separately scored each transcript, which included the records of the schizophrenic and manic patients. Two of these raters were blind to the patients' diagnoses and had never met the patients. The few differences that occurred in scoring were reconciled with the aid of a fourth experienced rater.

Data Analyses

The following Thought Disorder Index scores were examined in the three groups: 1) an assessment of quality of thought disorder provided by the 23 different categories of slippage; 2) a summary score obtained by adding all instances of thought disorder weighted on a 4-point severity scale, divided by the number of responses and multiplied by 100; and 3) a levels of severity score based on the number of instances of thought disorder at each of four levels of severity. Analyses of variance (ANOVAs) were performed on the summary scores and severity scores after distributions were normalized by using logarithmic and square root transformations, respectively.

Twenty-six qualitatively different categories of thought disorder were produced by dividing the inappropriate distance category into its four subcategories for separate analysis. These categories were consolidated into five factors by using a principal components analysis with iteration. The five factors had Eigen values above 1.69, and together they accounted for 48% of the thought disorder variance. ANOVAs were performed to determine whether the factors distinguished the patient groups. Student-Neuman-Keuls tests were also performed to assess simple effects for all ANOVAs where the null hypothesis could be rejected.

RESULTS

The most noteworthy finding was the differentiation of the three patient groups on quality of thinking disturbances. Whereas manic patients demonstrated predominantly flippant and overly combinatory thinking and schizophrenic patients produced predominantly peculiar verbalizations and incoherent responses, patients with right hemisphere cortical damage exhibited fragmented thinking characterized by defective integration, excessive qualification, disorientation, confusion, and vagueness. These differences occurred even though there were no significant differences in the amount of thought disorder.

Qualitative Differences in Thought Disorder

Table 1 shows the mean scores for the three patient groups on the five factors. Factor 1 is descriptive of combinatory thinking, factor 2 of fragmented thinking, factor 3 of idiosyncratic verbalization, factor 4 of expansive thinking, and factor 5 of arbitrary thinking.

It is striking that each of the groups was distinguished by prominence on one of the factors. On combinatory thinking the manic patients were the most productive. This factor reflects an inappropriately joc-

THE AMERICAN JOURNAL OF PSYCHIATRY

Conceptual and Methodological Issues in Comparative Studies of Psychotherapy and Pharmacotherapy, I: Active Ingredients and Mechanisms of Change

Irene Elkin, Ph.D., Paul A. Pilkonis, Ph.D.,
John P. Docherty, M.D., and Stuart M. Sotsky, M.D.

There has recently been an increased focus on comparing the effectiveness of drugs and psychotherapy in the treatment of mental disorders. The marked differences between these two treatment forms raise many conceptual and methodological problems for the investigator. In a two-part series, the authors discuss a number of these conceptual issues and their implications for research design, implementation, and interpretation of findings. Part I focuses on differences in the active ingredients and hypothesized mechanisms of change of psychotherapy and pharmacotherapy. Issues addressed include the need for standardization of treatments, adequate delivery of treatments, and controlling for factors other than the active ingredients of each treatment.

(Am J Psychiatry 1988; 145:909–917)

The two major forms of treatment for mental disorders are pharmacotherapy and psychotherapy. Over the last three decades hundreds of studies have examined the effectiveness of each of these forms of treatment. These have included studies comparing various drugs with each other and with placebo conditions and studies comparing various forms of psychotherapy with each other and with "no treatment," "waiting list," "attention-placebo," or other control conditions. A considerably smaller number of studies have examined pharmacotherapy and psychotherapy within the same research protocol, using the same patient samples and identical evaluation methods. These comparative efficacy studies have often been carried out by psychopharmacological researchers and, as Hollon and Beck (1) pointed out, have usually followed results establishing the efficacy of a new psychotropic drug. In the last two decades there has been increased interest in such comparison studies within the psychotherapy research field as well, due in part to the focus on evaluating the effects of specific psychosocial treatments for specific disorders (2–4).

The increase in comparative research has been an exciting development, as it promises eventual answers to critical clinical questions such as which particular treatment might most benefit a particular patient. It is important, however, to temper our enthusiasm in this area by acknowledging and explicitly addressing the many problems involved in carrying out and interpreting such comparative research. Although all treatment outcome research is complex and involves many methodological issues (2, 4–8), comparative studies of psychotherapy and pharmacotherapy involve a number of unique problems, resulting from the intrinsic conceptual and technical differences between these two forms of treatment.

We wish to emphasize that our goal is not to pit one treatment against another or polarize the adherents of different approaches. We recognize the value of both pharmacotherapy and psychotherapy, alone and in combination. Our experience in the NIMH Treatment of Depression Collaborative Research Program has made us keenly aware, however, of the inherent difficulties in designing, conducting, and interpreting results of studies that evaluate the effectiveness of both

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forms of treatment. Our intent is to identify some of the problems and to discuss ways of addressing them.

The problems encountered in such comparative research have rarely been addressed in the research literature. Over 20 years ago, Pokorny and Klett (9) identified a number of "technical problems" in this kind of research, including differences in appropriateness of patient samples, treatment goals, outcome measures, rates of action, and dropout rates and difficulties in maintaining the "blind." A few later investigators (1, 10–12) further addressed some of these concerns. In this paper we will focus on differences in active ingredients and purported mechanisms of change in pharmacotherapy and psychotherapy. In part II, which will appear in the next issue of the *Journal*, we will address differences in the nature of the expected treatment effects and related goals for treatment, differences in the time course of the treatments, and potential sources of bias in the research setting. We will discuss the ensuing practical problems and difficulties that must be faced in the design of a particular study, its implementation, and the analysis and interpretation of findings.

Much of this discussion will also be relevant for studies comparing the effectiveness of psychotherapy or pharmacotherapy alone to the effectiveness of a combination of psychotherapy and pharmacotherapy. We recognize, of course, that combining psychotherapy and pharmacotherapy is a common clinical practice. For the purposes of these two papers, however, we will focus on issues that are particularly salient for comparisons of specific pharmacotherapy and psychotherapy approaches, since it is useful, for scientific reasons, to start with a careful examination of the separate modalities.

Since the discussion will be largely based on our experience in designing and implementing the NIMH Treatment of Depression Collaborative Research Program (13), the points raised will be particularly relevant for research on outpatient depression and on short-term treatments. Many of the issues discussed will have broader relevance, however, and are important to consider in any study comparing pharmacotherapy and psychotherapy.

The starting point for our analysis of the issues involved in comparing pharmacotherapy and psychotherapy is the recognition that the core difference between them is the difference in their active ingredients and in the purported mechanisms by which they effect change. Psychotropic drug treatment is assumed to effect change mainly through biological mechanisms, initiated by the chemical that is administered to the patient. Psychotherapy, on the other hand, is assumed to bring about change largely through psychological mechanisms, initiated by one or another aspect of the interaction between therapist and patient. In comparative studies, it is essential to ensure the following: 1) the treatments are standardized, so the different active ingredients are actually present in their respective form of treatment and are not present in the other, 2) the active ingredients are being delivered in an adequate fashion, and 3) outcome differences cannot be attributed to other factors.

STANDARDIZATION OF TREATMENTS

To ensure that the active ingredients in a treatment are actually being delivered, it is necessary to define carefully the treatment condition, including the nature of the therapist's interventions. The absence of such clear definitions has made it extremely difficult to interpret findings from many psychotherapy research studies. As a result, there has been an increased emphasis on the "standardization" or "specification" of the technique variable in comparative psychotherapy outcome research (14, 15). Most prominent among the methodological advances in this area has been the development and use of manuals, which describe and provide guidelines for the conduct of particular forms of psychotherapy (16).

In a study comparing drugs and psychotherapy it is important that the pharmacotherapy condition also be defined with sufficient clarity to ensure the adequate delivery of the active ingredients in this treatment. For this reason, in addition to the use of manuals (17, 18) for the two psychotherapy conditions in the NIMH Treatment of Depression Collaborative Research Program, a manual was also developed for the conduct of the pharmacotherapy conditions (19). The major purpose of this manual is to present guidelines for adequate administration of the medication and for provision of conditions that will maximize the patient's compliance with the treatment regimen but will not overlap with specific psychotherapeutic approaches. (To further ensure that each of the treatments in the NIMH program was administered with adequate skill and consistency, therapist training, monitoring, and "certification" programs were devised [15, 20, 21].)

In the last analysis, however, the real evidence of whether the active ingredients of a specific treatment have been delivered can be found only in the records of the actual treatment. Investigators have begun to develop methods for measuring a therapist's adherence to a particular treatment approach from audiotapes of treatment sessions (22, 23, and unpublished study of Hollon et al.). It is also important to ascertain that each of the treatments has actually been conducted in a competent fashion (20, 21). This should help to ensure a fair comparison of the treatments being studied.

Delivering a treatment does not necessarily mean that it has been satisfactorily received or absorbed. The receipt of the active ingredients is considerably easier to assess in pharmacotherapy than in psychotherapy conditions. Various indicators of drug compliance are available, including pill counts and blood level analyses, and absorption distribution and metabolism can be measured chemically. There are no similar indicators of the "receipt" or "absorption" of psychotherapeutic interventions. It might facilitate the interpreta-

tion of comparative study results, however, if more attempts were made to assess patient "compliance" with psychotherapy. Possible indicators include such objective measures as number of missed sessions, number of minutes late to sessions, and completion of extra-session assignments. It is, of course, far more difficult to assess such variables as "resistance" or "acceptance" of an interpretation. As Morris Parloff has observed, there is no easy way to measure whether a patient has swallowed an interpretation or is holding it in his or her cheek.

ADEQUATE DELIVERY OF TREATMENTS

If we are to be fair in our comparisons of psychotherapy and pharmacotherapy conditions, it is essential that the proponents of each of the treatments agree that a study allows for the adequate delivery of their respective treatment. This concern raises a number of issues for the design and implementation of comparative studies, including the total length of the treatment period; the number, frequency, and length of sessions; and the characteristics and competence of the therapists administering the treatments.

Length of Treatment

Although much outpatient psychotherapy is actually very brief (24), psychotherapists, especially those with a psychodynamic orientation, have frequently been oriented toward long-term or open-ended treatment. It has, therefore, been difficult to compare these treatments with the generally shorter trials of medication, especially for affective and anxiety disorders. The introduction of a number of explicitly brief forms of psychotherapy has reduced the problems in this area and is responsible, in part, for the increased number of comparative studies of psychotherapy and pharmacotherapy. (This does not, of course, solve the more complex problems of comparing long-term psychotherapies with pharmacotherapy or, for that matter, with short-term psychotherapies.)

Nevertheless, one may face certain problems in determining the exact length of treatment. In designing the NIMH program, for example, we had greater consensus about the psychotherapy than the pharmacotherapy conditions. Previous research (12, 25) had suggested the adequacy of a 12- or 16-week treatment trial of the two forms of brief psychotherapy. Although most antidepressant drug trials have been much briefer, we found some disagreements among psychopharmacologists regarding the time necessary for an adequate trial of a tricyclic antidepressant, i.e., one that could be expected to result in full remission of symptoms and restitution of previous function. A 16-week treatment period was finally agreed on as an adequate trial by both pharmacotherapists and psychotherapists. What is most important here is that the duration be long enough that proponents of each approach feel that there has been sufficient time for the patient to benefit from treatment.

Number, Frequency, and Length of Sessions

Psychotherapies and psychopharmacological treatments typically differ in such variables as the number, frequency, and length of treatment sessions; psychotherapy has both more frequent and longer sessions. The question posed for the researcher is whether to establish strict consistency in these variables across treatment conditions or to allow them to vary as they do in practice. The general argument for consistency is based on the premise that these are extraneous variables and that allowing them to vary creates "noise" that makes it more difficult to compare the two treatment conditions. A more focused concern is that the greater amount of therapist-patient contact in one of the conditions might introduce a bias toward that treatment approach. The argument for variation follows from the view that the differences in these treatment characteristics are intrinsic to the treatment forms and are related to their presumed modes of therapeutic action. Thus, psychotherapies may require more frequent and longer sessions to allow for delivery of the active ingredients found in the patient-therapist interaction. The frequency and length of sessions in the pharmacotherapy condition can be more limited, since the active ingredient is presumed to be the medication, and the doctor's role is to provide optimal administration of the drug and enough clarity of direction and encouragement to ensure compliance. According to this view, an increase in the number or length of sessions for the pharmacotherapy condition might result in an increased emphasis on patient-therapist interactions and thus create an overlap with the active ingredients in psychotherapy.

There are no "correct" answers in resolving this dilemma; such decisions must always be made in the context of a particular study and the questions it poses. One must, in light of these questions, weigh the relative importance of maintaining the integrity of the treatments and of controlling possibly confounding variables. Perhaps most important is the necessity to take whatever decisions are made into account when interpreting the results of the study.

Appropriate and Competent Therapists

If each of the treatment conditions is to be adequately represented, appropriate therapists must be chosen to deliver them. However, the criteria for selection of appropriate therapists in one treatment approach may not be relevant for another. Problems of interpretation arise when differences between therapists in the different conditions are so great that it becomes difficult to attribute any differential results to the specific treatment approaches rather than to the therapists.

The most obvious difference that may be present

when comparing psychotherapy and pharmacotherapy lies in the professional discipline of the therapist. The administration of drugs requires the presence of a psychiatrist or other physician, while psychotherapy may be conducted by psychiatrists, psychologists, social workers, or other mental health professionals. This constraint on the range of therapists for pharmacotherapy conditions may create important differences in the types of disciplines involved in a comparative study. One could, of course, restrict a study to psychiatrists as therapists, but this choice would reduce the ability to generalize from the results in the psychotherapy conditions. The possible effects of discipline differences (for example, the effect on treatment response of the therapist's perceived authority and social prestige) need to be considered in the interpretation of comparative study findings.

There may also be more subtle effects on study results due to differences in the requirements for therapists in the different conditions, e.g., differences in the nature of the prior experience and training required for conducting the respective treatments. A complex psychotherapy requires, in general, a greater degree of training and expertise in interpersonal relationships than does the administration of a specific medication treatment. This may be especially true in a clinical trial that seeks to minimize the overlap of the pharmacotherapy with a psychotherapy condition and that provides detailed guidelines for the administration of the medication.

Further, to the degree that intensive personal training and expertise may be less necessary in the psychopharmacological condition, the amount of experience necessary for the conduct of the comparison psychotherapy condition may be underestimated. In the Schizophrenia Research Project (10) conducted by May and his colleagues, some attention was paid to possible differences in the experience necessary for the drug and psychotherapy conditions; a restriction was placed on random assignment so that therapists (psychiatric residents) with less than 6 months of training were not assigned any patients in the psychotherapy conditions. One might question, however, whether 6 months of experience plus regular supervision for study patients

> a 16-week treatment program that includes a pill-placebo condition. (13, p. 309)

As a final note on therapists' training and experience, it should be mentioned that there is actually little definitive information about the effects of these variables on the outcome of treatment or their differential roles in different forms of treatment (26). These are questions, however, that future research should address, within both psychotherapy and psychopharmacology and, perhaps especially, in the context of comparative studies. In the meantime, one resolution of this problem is to require the same minimum amount of relevant past training and experience for therapists in all treatment conditions and to achieve agreement on this minimum among the proponents of all approaches.

Since therapists may differ in numerous ways that could affect treatment outcome, some investigators have attempted to control for therapist characteristics by having all therapists participate in all treatment conditions. This strategy creates a neat design, since variance due to therapists can be extracted in the statistical analysis, providing a cleaner estimate of treatment differences. It is generally unreasonable to expect, however, that a therapist will be able to conduct different, "competing" treatments with the same degree of enthusiasm and commitment or even the same degree of skill (although this is, of course, an empirical question). It may be preferable to assign different therapists to different treatment conditions and ensure that they have comparable commitment, training, experience, and competence in their respective therapeutic approaches.

In interpreting the results of a study using different therapists for each treatment condition, it is important to remember that—no matter what attempts have been made to equate the therapists—what is being compared are not just specific techniques or interventions but, rather, different treatment packages. Each package is a composite of a treatment approach and the particular therapists who choose to practice it (and to



TABLE 1. Hypothetical Response to Psychotherapy, Pharmacotherapy, and Control Conditions

Treatment Condition	Percent of Patients Significantly Improved	
	Psychotherapy	Pharmacotherapy
Active	80	70
Placebo/control	50	30
Difference	30	40

Overlap of Treatments

In interpreting the results of comparative studies it is important to ensure that the purported active ingredients of one treatment are not also inadvertently present in the other. This is relatively easy in regard to chemical factors in psychotherapy, where patients may be prohibited from taking any psychotropic medications while in treatment (although one should always try to determine whether drug ingestion occurs despite such prohibitions). The situation is more difficult in a drug condition, where therapist and patient interactions do occur and may presumably play a role in bringing about change. In a comparative study it is necessary that psychopharmacologists be trained to refrain at least from those forms of psychosocial intervention presumed to constitute the primary and specific active ingredients of the psychotherapy. More discussion of these issues is provided in the section on the therapist-patient relationship.

Role of Control Groups

Psychotropic drug treatment and psychotherapy are such intrinsically different approaches that there may be differences in many aspects of treatment in addition to the specific medication and specific psychotherapeutic technique. Ideally, one would include separate groups that could control for the purportedly nonactive ingredients in each of the approaches. It would then be possible to answer more differentiated questions regarding not only the relative efficacy of the treatment packages but also the degree to which treatment effects are due to the hypothesized active ingredients. Table 1 illustrates this potential distinction. (Note that our hypothetical data assume a higher response rate in a "psychotherapy placebo" condition than in a "pill placebo" condition.) In this example, comparison of the rates of response to the two treatment packages indicates that psychotherapy is superior, but the opposite conclusion is drawn if the effects of the active ingredients are compared by examining the differences between the active and control conditions.

Unfortunately, a design including both a pill placebo and a psychotherapy placebo is not easy to execute, largely because of the difficulty of devising an adequate psychotherapy control condition. A major methodological advantage of psychopharmacological outcome research has been the availability of inert pill placebos that produce no physiological effects related to the treatment of the disorder and can thus control for the nonactive components in the drug condition. The task of developing a "placebo" condition for psychotherapy is far more complex, largely because of the problems in articulating what the active ingredients actually are in any form of psychotherapy. Although researchers have used "attention placebos" to control for nontechnique factors in the treatment situation, it is conceivable that the therapist's attention is itself one of the active ingredients in some forms of psychotherapy. For further discussions of the conceptual, technical, and ethical problems in devising psychotherapy "placebo" conditions, see the articles by Rosenthal and Frank (27), O'Leary and Borkovec (28), and Parloff (29).

Therapist-Patient Relationship

Rather than simply trying to control for the effects of nonactive ingredients in each of the treatments, it seems more productive to try to study those factors that may actually have an effect on outcome, either independently or in interaction with a specific treatment approach. Here we enter the realm of what have been called "nonspecific" factors in both the psychotherapy (30, 31) and pharmacotherapy (32, 33) literature. Because of the many different meanings of this term, however, it is more valuable to talk directly about the actual variables in which we are interested rather than about "nonspecific" factors, which might simply be nonspecified.

In the psychotherapy literature, the importance attributed to the therapist-patient relationship ranges from the view of some client-centered therapists and researchers (see review by Rice [34]) that it is the critical curative factor in therapy, through the classical psychoanalytic position in which it is the "ground" against which the "figure" of the therapeutic process unfolds (see reference 35), to the behavior therapists' growing acknowledgment of the role of the relationship in the therapeutic social learning process (36). Despite these variations in emphasis, virtually all current psychotherapy (and many behavior therapy) theorists and researchers do acknowledge the direct or indirect influence of the therapist-patient relationship on the outcome of treatment (37).

In contrast to the psychotherapy literature, current psychopharmacological outcome research does not generally address the role played by the therapist and his or her interaction with the patient, although some of the early psychopharmacological research literature suggested that nondrug factors, including therapist attitudes and "treatment set," may indeed play an important role in the efficacy of drug treatments (32, 38). One of the especially interesting studies of this period (39) found that aspects of the therapist's behavior, such as use of the patient's name, a patient-oriented body position, and vocal and facial animation, differentiated pharmacotherapists with high and low attri-

tion rates. Downing and Rickels (33), in summarizing some of the literature on the therapist-patient relationship in pharmacotherapy, suggested that the more intense the relationship, the less likely one is to obtain a significant difference between drug and placebo.

Despite these findings, it is easy to understand why less attention is paid to the doctor-patient relationship in pharmacotherapy. Here the presumption is that the active ingredients are to be found in the medication itself and that the relationship plays a minor role, mainly to ensure compliance with the medication regimen. With psychotherapy, on the other hand, it is generally hypothesized that various aspects of the patient-therapist interaction are involved in bringing about therapeutic change. A great deal of attention has been paid, for instance, to the relationship of the "therapeutic alliance" to psychotherapy outcome (40–45). It seems reasonable, then, to expect real differences between pharmacotherapy and psychotherapy in both the therapist's interventions aimed at developing the relationship and the actual relationship established. It is unlikely that we could completely control this set of variables by keeping them constant across the pharmacotherapy and psychotherapy conditions. Even if this were possible, we might not choose to do so, since they seem so integral a part of the treatments themselves.

How can we, then, address the role played by the therapist-patient relationship in comparisons of pharmacotherapy and psychotherapy? We can begin by acknowledging their potential importance in pharmacotherapy, as well as in psychotherapy, and then proceed to define and measure them. Manuals for various forms of psychotherapy (17, 18, 46, 47), although focused on therapeutic techniques, do attempt to specify the nature of the relationship considered necessary for the adequate administration of the treatment approach. Similarly, the manual developed for the pharmacotherapy conditions in the NIMH program (19) specifies guidelines for the provision of support and encouragement of the patient (as well as direct advice if necessary) to ensure compliance with the treatment condition and the maintenance of optimism.

It should be pointed out that the general lack of attention to relationship factors in pharmacotherapy research may result in quite different conditions among studies in the kind of relationship that is actually offered (e.g., what has sometimes been called "warm drug" versus "cold drug"). In terms of acceptability to both patients and therapists, a "warm" drug condition, in which the therapist explicitly offers support and encouragement, is likely to be preferred, but it must be acknowledged that such a condition provides a conservative test of the effectiveness of the psychotherapy in comparison to drug treatment. On the other hand, an extremely neutral or "cold" drug condition may create problems in regard to compliance with the treatment regimen and thus not provide an adequate test of the drug condition.

Interpretation of results in comparative studies, in terms of both attrition and outcome, is made more problematic to the extent that relationship issues are not addressed or monitored in medication conditions. It may be difficult to determine if pharmacotherapy is, in fact, a form of combined treatment (a supportive, communicative relationship along with an efficacious drug) as opposed to a medication-only condition. It is likely that a number of studies in the psychopharmacology literature included a sizable psychotherapeutic component, transforming some drug versus placebo comparisons into drug plus psychotherapy versus placebo plus psychotherapy comparisons. The wide variability in both active drug and placebo response rates among studies of antidepressant drugs may be partially due to the variability in the amount of psychotherapy offered along with the drug.

TABLE 2. Hypothetical Response to Psychotherapy and to Pharmacotherapy With and Without Therapist Support

Treatment Condition	Percent of Patients Significantly Improved		
		Pharmacotherapy	
	Psychotherapy	Without Supportive Relationship	With Supportive Relationship
Active	70	70	80
Placebo/control	50	30	60
Difference	20	40	20

Table 2, again using hypothetical data, illustrates the different conclusions that might be drawn from a study comparing drug and psychotherapy, depending on whether a supportive relationship is offered in the drug condition. In this example, the drug is found to be more effective than psychotherapy only in the condition in which it is embedded in a supportive relationship, although the effects of the active ingredients in the medication are most pronounced in the drug condition that does not include therapist support.

In addition to defining the relationship components of the different treatment approaches and training therapists to deliver them, it is important to measure the actual relationships that are established. At the present time, appropriate measures are more readily available for psychotherapy than for pharmacotherapy; to our knowledge, no instrument has yet been developed, for example, to measure the "therapeutic alliance" in pharmacotherapy, although the concept is a relevant one (48). The development and application of such measures could lead to a better understanding of the total treatment packages delivered and to the relative contributions of specific treatment approaches and relationship factors in comparisons of psychotherapy and pharmacotherapy.

Patient Attitudes and Expectations

In any treatment outcome study, differential attitudes, expectations, and preferences for one or another treatment may be influential. There has been considerable interest over the years in patient expectations

about treatment, the relationship of these expectations to sociodemographic factors, and the effects of expectations on both attrition and outcome of treatment (24, 49). Most relevant for studies comparing psychotherapy and pharmacotherapy are the expectations and preferences that patients may have for one or another of these treatment forms. Although to our knowledge, this issue has not been studied directly in the context of a comparative study, other research studies suggest that psychiatric patients differ in the extent to which they expect the therapist to be directive and to have a medical orientation and that these differences may relate to variables such as social class (50, 51). Perhaps most interesting is the finding that a patient's remaining in treatment may be related to the congruence between his or her expectations and the treatment actually received (52, 53).

Variation in the percentage of patients in a study who expect and/or prefer either drug treatment or psychotherapy might influence comparative outcome findings. For example, if a particular facility is known for providing psychotherapy, it is possible that patients coming to that facility prefer this form of treatment and may be more likely to remain in a psychotherapy condition and to profit from it. In this same vein, one can speculate that, in the study by Weissman et al. (25), the high percentage (32%) of patients assigned to the psychotherapy-alone condition who dropped out before the first session might be due in part to the patients' expectations of receiving drug treatment at the Yale Depression Research Unit. Early attrition due to patients' preferences for another form of treatment emphasizes the importance of not pressing prospective subjects to participate in a comparative trial if they strongly prefer a specific form of treatment. (Particular care should be taken when research protocols provide free treatment, which may encourage patients with limited financial means to accept treatments they would not ordinarily seek.) In interpreting findings in comparative studies, we must remember also that they are limited to patients who accept randomized assignment to either of the treatment forms.

Even after the exclusion of patients with strong preferences, the issue of patient expectations does not disappear. Some patients, for example, will agree to participate despite having preferences for one or another form of treatment, hoping that the "flip of the coin" will come up in their favor. Our experience and that of other investigators has been that a few of these patients drop out before treatment actually begins; others "give it a chance" but drop out relatively early in the treatment process. Systematically gathered information on patients' expectations and/or treatment preferences and careful specification of patients' reasons for dropping out of treatment would facilitate an understanding of such attrition data.

To take the argument even further, patients with strong preferences who nonetheless accept assignment to and remain in nonpreferred treatment may be discouraged from the outset about the potential for benefit from a therapy in which they have little faith. Ambivalence about therapy may affect compliance with the treatment, leading patients to refuse to take their medication, to neglect homework assignments in cognitive and behavioral therapies, and to "forget" or cancel psychotherapy appointments. Such patients may express disappointment through negative attitudes toward their therapists and resistance to the therapeutic process, and these attitudes may in turn generate a negative response from the therapists. Thus, it is important to recognize that a comparative study conducted with a group of patients who have high expectations for one of the treatments could, in a number of ways, bias the results in favor of that treatment. It would be ideal, of course, to balance the sample and individual treatment groups on this variable; if that is not possible, expectation data might prove useful in understanding both process and outcome findings.

What is most important, in considering patient expectations as well as the other variables discussed in this paper, is the recognition of the ways in which they could potentially bias comparative outcome findings. Wherever possible, studies should be designed to minimize such sources of bias. Where this is not possible, the potential influence of these variables should be considered when interpreting and generalizing from the findings.

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Psychiatric Decision Making in the Emergency Room: A Research Overview

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In an overview of the research on psychiatric decision making in the emergency room, the authors discuss studies done between 1963 and 1977, which suffered from an overreliance on univariate statistical techniques, problems with the reliability and validity of the instruments used for data collection, and the lack of alternatives to hospitalization for emergency room patients. More recent studies of emergency room decision making are then reviewed, with particular attention to those that had multivariate statistical designs. The article concludes with a synthesis of the research findings to date and recommends multivariate approaches and choices of variables for future studies.
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Over the past 20 years, the urban psychiatric emergency room has increasingly become the chief entry point for individuals seeking mental health care. In particular, the emergency room now functions as virtually the only treatment site for those chronically mentally ill individuals who represent the legacy of deinstitutionalization. The referral decisions of emergency room clinicians have become critical to successful intervention with such patients: "For the troubled individual the decisions made during the emergency room visit determine the choice of a subsequent treatment plan and often influence the course of the problem or illness" (1, p. 1). Research into the emergency room decision-making process therefore plays an important part in better understanding and treating this large and clinically challenging population.

This article is intended to provide the reader with an updated review of research on decision making in the emergency room. We begin by discussing earlier research efforts (between 1963 and 1977) and offering a critique of the methodology of this work. We then review the research published after 1977, with particular focus on recent multivariate statistical studies. The article concludes with recommendations for the design of future studies on emergency room decision making.

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THE EARLY RESEARCH

Research interest in emergency room decision making is relatively new. The first in-depth research (2–4) appeared in 1963, the year that the Community Mental Health Centers Act was passed. As the national policy of deinstitutionalization began to exert pressure on emergency room facilities and resources, researchers became interested in emergency room decision making and in developing a model "aimed at relatively rapid evaluation, containment, and referral of the patient in crisis" (1, p. 9).

The first group of studies, which emerged from approximately 1963 to 1977, sought to identify the domains and individual variables that contributed significantly to decisions to hospitalize. These domains and variables included demographic factors such as age, sex, and race; clinical factors such as diagnosis, symptom severity, and dangerousness to self or others; clinician factors such as discipline and level of experience; and other family and system variables. By uncovering and analyzing variables that proved to be significantly associated with certain dispositions, this first group of studies assisted hospitals and clinics in their efforts to fashion effective emergency programs. (The term "disposition" in this context refers to the range of possible outcomes available to a presenting patient, for example, inpatient hospitalization, placement in a residential facility, referral to outpatient care, or discharge home.)

The early research in emergency room decision making was critically reviewed in 1980 by Gerson and Bassuk (1). These authors comprehensively examined the relevant literature published between 1963 and 1977 and set out the major research findings for key individual variables of the kinds we have just mentioned.

While the initial group of emergency room studies successfully identified a large number of individual variables that were significantly correlated with the decision to hospitalize, these studies suffered from a number of distinct methodological problems. First, they relied exclusively on univariate statistical tech-

niques (chi-square, t test) to ascertain which variables were significantly related to disposition. The use in many studies of a large number of such significance tests increased the possibility of experimentwise error (i.e., significant results due to chance alone). Furthermore, the studies provided no overall measure of how well the variables *as a group* differentiated the alternative dispositions. Multivariate statistics were not used to examine the interactions between variables or to identify and prioritize the key variables that together accounted for the disposition selected. For example, if both diagnosis and symptom severity were found, separately, to be significantly related to hospitalization, the interaction between them could not be examined. It remained unclear whether a patient with a diagnosis of a serious disorder but less severe symptoms was more likely to be hospitalized than a patient with a less serious disorder but extremely severe symptoms.

In short, the early literature presented a somewhat bewildering and overlapping array of significant individual variables. It remained unclear which interactions between variables took precedence and how the decision-making process as a whole worked (5, 6).

Second, very few of the early studies established the reliability of the different data-collecting instruments that were used in their particular research designs. Thus, problems of measurement consistency and stability, which too often went unacknowledged by the various authors, compromised to some extent the validity of these studies.

Third, the methodological value of the early studies has now been lessened by the increasing complexity of emergency room decision making. In the early studies, the decision about the disposition for a patient almost invariably involved a simplistic dichotomy: to hospitalize or not to hospitalize. While such limited choice characterized emergency room dispositions of the 1960s and 1970s, modern psychiatric dispositions, by contrast, increasingly involve a much wider range of alternatives with varying degrees of restriction. At a large urban facility, the spectrum of choices may range from the most restrictive (inpatient hospitalization) through a series of less restrictive options (24-hour observation, supervised residential programs, and a wide array of outpatient referral possibilities) and only then conclude with discharge home. Used in research, this broader spectrum of outcomes captures the clinical reality to a greater extent than did the simplistic, either/or alternatives of the earlier research.

Finally, in the interest of fairness, any critique of the earlier emergency room research must also acknowledge the methodological context of that research. Many, if not most, of the early studies were conducted by busy clinicians who had the challenging task of ensuring the integrity of their research designs in the turbulent setting and among the varied personnel of the emergency room. The limited choice of dispositions available to these researchers has already been mentioned; emergency psychiatry then was not as vitally concerned as it is today with alternatives to hospitalization and decreasing the length of stay. In addition, small sample sizes, as well as general lack of sophistication about multivariate statistical designs, limited researchers to basic univariate inquiry.

THE MORE RECENT RESEARCH

In the last 10 years, research on emergency room decision making has taken one of two different forms. Some of the work (7–10) has simply replicated, with increased sophistication, the straightforward univariate designs of the past. During this same period, however, a number of studies (5, 6, 11, 12) have broken with convention and used multivariate designs. Such studies have often used univariate tests and then followed them with multivariate analyses that identified the variables which, when taken together, accounted for the decision process.

Our literature review updates the work of Gerson and Bassuk (1), and examines decision-making research—univariate and multivariate—between 1978 and the present in each of the following domains of variables: demographic, clinical, clinician, family, and system. The new multivariate designs are discussed in greater detail after the general review.

Demographic Variables

As reported by Gerson and Bassuk (1), the age of the patient, by itself, has not been consistently related to disposition. Whereas many earlier studies examined this possible relationship, only two (13, 14) reported significant findings. These two studies found that significantly greater proportions of patients were hospitalized as age increased. Another study (4) found that hospitalization rates increased with age only for patients with diagnoses of alcoholism or chronic brain syndrome. In the more recent research, not one study found that age was significantly related to disposition (5, 7, 8, 15–17).

While most research shows that more women than men use psychiatric emergency services, most studies have failed to relate sex to disposition. Two earlier studies (2, 18) did find that men were significantly more likely to be referred for inpatient treatment. The current research largely confirms the earlier nonsignificant findings (5, 8, 15–17). However, one study (7) found that women were more likely to be referred to an overnight hospital for observation than to be directly hospitalized.

Race is also not a significant determinant of decisions to hospitalize (1), although one early study (19) found that nonwhite patients—specifically, nonwhite women—were more likely to receive treatment in the emergency room "as needed" than to receive inpatient treatment. In recent research (5, 7, 8, 15–17), race has remained a nonsignificant factor in decisions about the disposition of emergency room patients.

The religious affiliation of the patient has not proven to be relevant to disposition in either early or recent emergency room research (15). However, one of the later studies (8) did find that affiliation with the Protestant faith was related to nonadmission.

Clinical Variables

Diagnosis has consistently been related to disposition, and almost all researchers would agree that it is an important determinant. However, studies disagree about which diagnoses lead to hospitalization (2, 13–15, 18). Friedman et al. (6), for example, noted that admission rates for schizophrenic patients seem to be in part determined by local beliefs about where these patients are best treated. As we shall discuss, symptom crisis and dangerousness have emerged as more important determinants than diagnosis.

The current research confirms the significance of diagnosis in emergency room decision making (5, 7, 15). However, again, patients with more acute symptoms tend to be hospitalized. In one study (5), acute psychotic episodes, schizophrenia, and bipolar affective disorders were related to hospitalization; patients with personality disorders (without psychotic features), on the other hand, tended not to be hospitalized (5, 7). In another study, which involved violent patients (10), a diagnosis of schizophrenia was one of only two variables relevant to admission. In one of the more recent studies (8), diagnosis was not found to be significant. In a reliability study (9), emergency room diagnosis (in comparison with subsequent ward diagnosis) was accurate for broad diagnostic categories such as psychosis, depression, and alcoholism, but not for more specific subtypes of mental illness such as schizophrenia and bipolar affective disorder.

In summary, diagnosis clearly relates to disposition on a univariate level. An important concern is whether severity of symptoms is the real underlying factor; the multivariate studies that we review later in the paper help disentangle the significance of diagnosis from the significance of symptoms. The reliability of emergency room diagnosis also remains a problem in studies that do not use standardized diagnostic interviews. A diagnosis of a severe disorder could be assigned to a patient as an artifact of the disposition chosen and could therefore be influenced by unseen administrative and legal factors.

As we have just mentioned, prominence of symptoms, along with dangerousness, is probably the single most important clinical determinant of the decision to hospitalize (20). Only one early study (21) found otherwise, and its discrepant results were probably the result of an unusual patient sample that manifested uniformly severe symptoms.

The importance of symptom severity is corroborated in the recent research (5, 6, 8, 15). In one study (6), "schizophrenic symptoms" (never explicitly defined) proved highly significant ($r^2=0.45$, $N=125$, $p<0.0001$), according to discriminant function analysis, and was clearly the more prominent of the two variables that predicted admission. Similarly, in a study (10) involving 62 violent patients screened from a total presenting sample of 416, the psychotic symptoms variable was one of only two relevant variables and was significant ($\chi^2=28.45$, $N=62$, $p<0.0001$). In a study (8) where the entire sample had engaged in behavior dangerous to self or others, symptom severity was significant, albeit only at $p<0.09$ ($N=99$, chi-square or t test).

A significant direct relationship between dangerousness and hospitalization was reported in all but one of the earlier studies that examined this variable (1). A possible experimental artifact is that dangerousness is the legal criterion for commitment; some authors have posited that clinical assessments of dangerousness merely reflect legal justifications for hospitalization decisions already made. As Gerson and Bassuk (1) pointed out, a comparative study of voluntary and involuntary patients might help resolve this problem.

Such a study has appeared in the more recent literature (22). The authors found that involuntarily committed patients were significantly more assaultive before hospitalization than voluntary patients (gamma=0.72, $N=258$, $p<0.05$), suggesting that the clinical assessments of dangerousness may be valid.

Other recent research confirms the importance of dangerous ideation and behavior in determining the need for hospitalization (5, 7, 8). Active suicidal and/or homicidal ideation was the second of the two key predictor variables in the multivariate study we have already cited (6). However, the same authors, in an earlier, related univariate study (15), pointed out that although they were important, homicidal and suicidal ideation and behavior were not sole or sufficient criteria for admission. We feel that it is important to evaluate suicidal and homicidal ideation versus suicidal and homicidal behaviors differentially, in order to better understand which more profoundly influences the decisions of intake clinicians.

A patient's previous psychiatric history has also proven to be an important determinant of disposition (14, 18, 21). A 1975 replication (23) of the Mendel and Rapport 1969 study (21), however, found that a history of hospitalization was not linked to the emergency room decision to admit.

The more recent research (5, 8, 15, 16) confirms that previous psychiatric history is an important decision-making factor, although not as significant as symptoms or dangerousness. In one study (16), patients with a history of previous psychiatric hospitalization were twice as likely as first-time patients to be admitted. In the two recent multivariate studies reported, previous hospitalization ultimately became a key variable in one (5) but not in the other (6).

Clinician Variables

Earlier research has tended to show that psychiatrists hospitalize patients at higher rates than do social workers or psychologists (1, 21, 23). However, these

findings also show that psychiatrists hospitalize at significantly lower rates than do third-, second-, and particularly first-year psychiatric residents. In the Mendel and Rapport study (21), staff social workers hospitalized the fewest patients (25% of all patients evaluated), followed by staff psychiatrists (37%), residents (48%), and psychologists (50%). In the replication study by Streiner et al. (23), the pattern continued: social workers hospitalized the fewest patients (25%), followed by psychologists (26%), nurses (30%), staff psychiatrists (39%), residents (40%), and family practitioners (45%). In explaining their results, Mendel and Rapport (21) indicated that social workers—and, by implication, other nonphysician professionals—were more aware of family and community resources available to patients; furthermore, the necessity of obtaining a psychiatrist's approval for admitting a patient to the hospital led nonphysician professionals to seek alternatives to admission. To our knowledge, since the study by Streiner et al., there has been no further research on the variable of the clinician's professional discipline.

With respect to clinician experience, the earlier studies (18, 21, 23) found an inverse relationship to the number of referrals for inpatient care. Decision makers who had had less than 6 months' experience hospitalized a significantly larger number of patients than did the more experienced clinicians (21). Professionals with more than 3 years of experience hospitalized the fewest patients (32% of those presenting), followed by those with 1–3 years (41%), 6 months to a year (43%), and 0–6 months (49%). The authors suggested that the inexperienced clinician lacks the confidence to make less restrictive dispositions and chooses hospitalization as a means of limiting decision-making responsibility (21).

Current research confirms the earlier findings regarding clinician experience and at the same time offers a new theoretical understanding of those findings. In the study by Meyerson et al. (16), psychiatrists with less than 2 years' experience admitted 33% of the patients evaluated, whereas psychiatrists with greater experience admitted only 16%—a significant difference ($N=1,551$, $p<0.001$, chi-square test). The matter of experience was best illustrated in the comparison of decisions in cases involving evidence of hallucinations. While the overall admission rate was 23%, for patients with hallucinations it ballooned to 49%. The entire increase was accounted for by the inexperienced clinicians' admission of 69% of the patients reporting hallucinations, whereas the experienced clinicians hospitalized 21%.

The most interesting finding of the study by Meyerson et al. was that a clinician's choice of disposition may be as much related to milieu and specific training as it is to years of clinical experience. When the training program was modified and second-year residents were introduced into a more closely supervised, structured setting—involving more exposure to alternative treatment options—there was a dramatic drop in admission rates, and decision-making patterns approached those of third-year residents and attending physicians (16).

The literature has generally shown that the therapist's positive emotional response to the patient is an influential, albeit not decisive, variable (13, 18). Tischler (13) found that "likeable and interesting" patients, whom the examining residents could choose to follow up, were more likely to be referred for outpatient services. At least one early study (24) found that therapeutic rapport per se was nonsignificant.

Of the recent investigators, only Apsler and Bassuk (5) have addressed the rapport variable. The factors of therapist comfort and rapport between therapist and patient were significant in discriminating hospitalized from nonhospitalized patients ($N=617$, $p<0.001$, chi-square and t tests). The patient's expression of appreciation was also significant ($p<0.01$), as was the therapist's perception of the patient as "interesting" ($p<0.01$).

Family Variables

The availability of family, peer, and community supports and resources has uniformly influenced disposition. The presence of social resources lessens the likelihood of admission (21, 23), sometimes dramatically (21), whereas single patients and unemployed patients are more likely to be admitted (2, 13, 14). In fact, almost all the studies indicated that hospitalization could have been avoided if there had been a more supportive and protective social milieu (1).

The findings of two of the more recent studies have been mixed with respect to the importance of social supports. In one of these studies (8), "no place to stay" was significant ($N=99$, $p<0.02$, chi-square test), whereas in the other (15), the patient's current social or work adjustment was clearly related to admission. However, social support did not emerge as a significant variable in the Apsler and Bassuk study (5), and marital status proved nonsignificant in another (7).

A relatively overlooked variable is the extent of family members' influence on the disposition decision. In his landmark article, Tischler (13) found that in approximately 60% of cases, the family is either present or is contacted before the decision is made. He also found that the final disposition deviated from the resident's perception of the family's wish in only 11 instances (13%). A subsequent study (25) confirmed this phenomenon: the presence of family or friends who encouraged hospitalization was significantly correlated ($r=0.54$, $N=34$, $p<0.01$) with the decision to admit.

Although recent research has not explicitly focused on family presence and pressure, the importance of the variable can be inferred from several studies (5, 6, 15). In the two studies by Friedman et al. (6, 15), the breakdown of patients' admission rates according to means of arrival at the hospital (alone, with family, or with police) was highly significant ($\chi^2=30.12$, $N-184$, $p<0.0001$). In the follow-up multivariate study (6),

being accompanied to the hospital remained a critical variable in the multiple regression analysis. The same variable achieved univariate significance (N=617, $p<0.003$, chi-square test) but not multivariate significance in the Apsler and Bassuk study (5). One can infer that the presence of family and a possible family agenda remain vital aspects of the clinician's decision-making calculus.

System Variables

Although it seems obvious, it should nonetheless be emphasized that a system which features alternatives to hospitalization, such as day hospitals or case management programs, is less likely to hospitalize (12, 20). Research on alternatives to hospitalization (11) bears out this conclusion.

A number of previous studies focused on system factors, such as hospital census, day and time of admission, and source of referral, in analyzing emergency room decision making. The results to date have been conflicting. In the Mendel and Rapport study (21), daily hospital census level did not prove to be significantly related to disposition, although there was little fluctuation during the data collection period. On the other hand, the authors did find that day and time of admission were significant; there were twice as many inpatient admissions between 5:00 p.m. and 9:00 a.m. on weekdays and all day on weekends. These results were not replicated by Streiner et al. (23). One may surmise that the unique circumstances of a particular institution largely influence the timing of admission decisions.

Court and police referrals appear to be significantly related to decisions to admit (22). It seems likely, particularly in our litigious time, that intake decisions will be strongly influenced by relevant judicial and police concerns about patients. One study (8) found that "emergency/court referral" was the single most critical variable related to admission.

On the whole, the current research has largely neglected study of potential system factors. In future research, system factors such as police and judicial referral should receive much more attention, as should the fluctuating influence of circumstances such as availability of beds and funding status.

RECENT MULTIVARIATE STUDIES

As we have suggested, the most important recent development in research on emergency room decision making has been the advent of multivariate statistical designs. In the late 1970s, for the first time, research on emergency room disposition examined the interactive significance of variables and identified those few variables which, acting together, largely accounted for differences in disposition. To date we have located four such studies.

Possibly the first multivariate analysis of emergency room decision making was published by Feigelson et al. in 1978 (12). In that study the authors sought to isolate the demographic, clinical, and institutional determinants of hospitalization. Over the course of a month, information was elicited from 200 subjects, presenting at four separate facilities, on demographic variables such as age, sex, and race and on clinical variables such as presence or absence of psychosis, chronicity, history of previous hospitalization, and Global Assessment Scale (GAS) rating.

The study used a stagewise multiple regression analysis, with the decision to hospitalize as the dependent variable. Clinical variables played the most powerful role in the decision to admit, followed closely by service facility. Of the clinical variables, the GAS score emerged first ($r^2=0.05$, N=200, $p<0.01$), followed by previous hospitalization ($r^2=0.09$, N=200, $p<0.05$). When the clinical variables were controlled, the service facility variable appeared most significant ($r^2=0.18$, $p<0.01$).

The most interesting finding in the study by Feigelson et al. was the significance of the institution. Decisions to hospitalize reflected not only clinical factors but also available program alternatives at the various facilities. The authors noted that the two emergency rooms with the lowest admission rates were staffed by attending psychiatrists, not residents. This finding corresponded to Mendel and Rapport's findings of a decade earlier (21). In addition, the same two emergency rooms had crisis intervention services, whereas such programs did not exist at the other two emergency rooms. Thus, the specific facility's staffing patterns and program alternatives were critical institutional factors influencing the decision to admit (12).

Although it included a path-breaking use of multivariate analysis, the study by Feigelson et al. had some limitations. For one, it limited the dependent variable to one outcome—hospitalization—rather than providing a range of differentially restrictive outcomes. Second, the design did not offer any kind of cross-validation of the multivariate results. Finally, the study did not use clinician or family variables in the analysis. The study's demographic and clinical variables ultimately explained only about 20% of the variance, so the absence of clinician and family variables may well have accounted for the modest level of explanation.

Another multivariate approach to emergency room decision making was taken by Apsler and Bassuk in 1983 (5). In that study, the authors sought to contrast the individual and the cumulative impact of demographic, clinical, and clinician variables on the decision to hospitalize. The first phase of the design was univariate: the authors tested the individual significance of a range of independent variables. The second phase involved the use of multivariate statistics to determine how well all the significant individual variables, when taken together, differentiated hospitalized from nonhospitalized patients.

In analyzing the data, the authors created four models of decision making, each corresponding to the

idiosyncratic pattern of a particular intake clinician. Using multiple regression analysis, the authors successfully accounted for a high percentage of the dispositions of three of the four clinicians. Overall, the four models, which had very limited criteria relative to the number of patients classified, correctly classified 90% of all the patients.

The great value of the Apsler and Bassuk study was that it revealed how factors important in the univariate analysis ultimately proved to be statistically unimportant. After multivariate analysis, most of the variables that had achieved significance in the univariate analysis were excluded from the final list of criteria. This final list included different combinations, for the respective clinicians, of diagnosis, suicidal and homicidal behaviors, and emergency room recidivism. The small number of emergent discriminating variables corresponds heuristically to the emergency room psychiatric setting, where clinicians must make rapid judgments on the basis of small amounts of information. Apsler and Bassuk's model seems to have practical value in evaluating emergency room decision making, both generally and on the level of the individual clinician.

With respect to the study's limitations, Apsler and Bassuk limited the dependent variable to admission and chose not to cross-validate their multivariate results. They also failed to report the reliability of the data and clinical instruments that were used. Finally, the findings were derived from a small number of clinicians, heightening the potential effects of idiosyncratic and nongeneralizable factors.

Like Apsler and Bassuk, Friedman et al. (6) used a multivariate design to eliminate the overlapping findings and confusion created by research that uses a host of univariate social, psychiatric, and community variables. The authors chose clinical, social, and demographic variables that had proven to be significant in an earlier univariate research effort (15). For purposes of subsequent cross-validation, they randomly divided their original sample of 188 emergency room patients into two groups: an exploratory group (N=125) and a cross-validation group (N=63). In the exploratory group the relationship between admission and the 12 significant univariate variables was examined by means of a stagewise multiple regression analysis. Of the 12 variables, only five made significant contributions ($p<0.05$) to the total predicted variance (r^2) of 0.49 (N=125). Of these variables, set forth along with their respective percentages of predicted variance, four were clinical and one was institutional: severity of schizophrenic symptoms (41%), how the patient came to the hospital (30%), active suicidal or homicidal ideation (18%), primary diagnosis (6%), and method of coping (5%).

For cross-validation, the same five variables were used in examining the second set of 63 subjects. Only two variables, both clinical, reliably determined admission: severity of schizophrenic symptoms (82%) and active suicidal and/or homicidal ideation (18%).

The results of the Friedman et al. study were similar to those of Apsler and Bassuk in that, after multivariate analysis, a very small number of consistent clinical variables emerged as critical to disposition. In the Friedman et al. study, two important and clinically reasonable variables accounted for a third of the variance. While a sizable amount of the variance was left unaccounted for, the study made evident the primacy of clinical variables in the decision-making process.

The Friedman et al. study is another example of how a multivariate design can penetrate to the reality of emergency room decision making in a manner impossible for univariate studies. The study also showed the importance of cross-validation as a means of further refining the multivariate findings. What the study lacked, as did the other multivariate studies we have discussed, was a broader range of possible dispositions.

A markedly different multivariate approach to emergency room decision making was taken by Sagg in 1985 (11). She sought to identify the independent variables predictive of three distinct and successively less restrictive dispositions: hospitalization, an emergency residential program, and an outpatient referral program. The author was interested in determining whether the characteristics of the patients in the three disposition groups varied sufficiently to justify the different dispositions.

The study sample involved 225 publicly funded patients who received emergency room evaluations. There were 75 patients in each of the three disposition groups (hospitalization, emergency housing, crisis outpatient care). Each of these three groups was divided into an exploration group and a cross-validation group. The three exploration groups were then compared in terms of demographic, clinical, and institutional variables to identify the specific variables that significantly differentiated the groups. In addition, all of the patients were rated on an index measuring the need for hospitalization to examine the relationship between assessed need and restrictiveness of the treatment disposition.

Univariate analysis resulted in a list of 17 variables that significantly differentiated the groups. These variables included age, sex, education, employment status, psychotic diagnosis, psychoticism, and source of referral. The 17 initial predictors were then assessed by means of a stepwise discriminant function analysis to ascertain their interaction and combined effect in predicting membership in a disposition group. The emergent function revealed that the patients most likely to be hospitalized were the most psychiatrically impaired, were diagnosed as psychotic, were female, were highly educated, and were not self-referred. Other variable models were obtained for the two other dispositions. Overall, 76% of the cases were correctly classified.

With the cross-validation sample, the result was that 63% of the cases were correctly classified according to disposition, a percentage that, again, was still notably better than chance despite the inevitable shrinkage in effect size.

The value of the Slagg study is its consideration of a wider spectrum of dispositions. Such an approach is much closer to the reality of the modern emergency room setting, where clinicians almost always have several disposition alternatives available. The study also coupled univariate and multivariate analyses and incorporated cross-validation as an additional control. The major limitation of the study, however, was the psychometric weakness of the clinical variables and the absence of clinician and family variables altogether.

RECOMMENDATIONS FOR FURTHER RESEARCH

Research on psychiatric emergency room decision making is currently receiving considerable interest, as attested by the number of new, creative research designs. In this final section, the present status of the field is summarized and some recommendations for future research are offered.

Emergency room decision making is presently the subject of much univariate research. Studies have assessed virtually every variable conceivably related to disposition and have frequently found significance. As the multivariate studies have suggested, however, such significance is often ultimately spurious; only a few variables, usually clinical measures, emerge as true determinants in the decision-making process. Therefore, future univariate research, if conducted at all, should focus only on variables that have consistently proven to be significant under multivariate analysis. These proven variables include severity of symptoms (5), particularly psychotic symptoms (6, 12); suicidal and/or homicidal ideation (6); and previous hospitalization (5, 12). Other important variables include an established measure of global level of functioning (12), diagnosis (5, 6), and source of referral (5, 6).

If at all possible, however, a multivariate design should be adopted from the outset. A multivariate design avoids the validity risks of univariate approaches by analyzing the interactions among all variables and identifying the key variables that together account for the disposition. Moreover, a multivariate design can select and prioritize a wide range of variables without having to incorporate a preliminary univariate analysis. Through procedures like stepwise regression, one can enter a large number of potential predictor variables and emerge with the combination of hierarchically ordered variables that best accounts for the decision process. The disadvantage of multivariate designs, of course, is that they require a large number of subjects. However, obtaining a sufficiently large sample usually should not pose a problem for the emergency room researcher.

For these reasons, future emergency room research needs to take a multivariate form if the realities of emergency room evaluation and disposition are to be discerned and hospital policy is to be formulated accordingly. The following recommendations are offered as guidelines for such research.

1. A multivariate design should be used from the beginning. A univariate analysis can precede the multivariate analysis, as it has in previous studies, but it is unwise and usually unnecessary.

Cross-validation serves as a useful check on generalizability. If at all possible, the cross-validation group should be drawn from an entirely distinct subject sample and setting. However, a split half procedure is also acceptable.

A number of models now exist for emergency room multivariate analysis. A straightforward approach is simply to isolate the two or three key variables critical to disposition of patients (6, 12). This approach would allow program evaluators to ensure that emergency room intake clinicians as a group are proceeding according to sound principles of evaluation and referral.

A second multivariate approach, that of logistic analysis, permits a closer understanding of the decision making of individual clinicians (5). Key determinants of disposition are derived for the individual decision maker. Such an analysis can reveal individual decision-making styles and, perhaps more important, any marked inconsistencies among clinicians.

Most recently, a third multivariate emergency room model, that of discriminant analysis, has emerged. It analyzes data to discern the independent variables that predict what a patient's disposition will be (11). By using discriminant analysis researchers can determine whether dispositional group differences are justified on the basis of alleged clinical indications.

2. The predictor variables should be drawn from the demographic, clinical, clinician, family, and institutional domains we have discussed and should be chosen in terms of their historically proven significance to disposition.

The instruments that provide the data for these different variables should have reported reliability and validity, so that the results are generalizable and comparable across contexts and investigators.

3. Studies should seek to predict the wide range of dispositions actually available to the clinician. Most previous research has artificially collapsed the decision-making process into the two alternatives of admission and nonadmission. By considering outcome more broadly as a range of differentially restrictive alternatives, a study will better approach the actual situation of the decision maker and thereby achieve more meaningful results.

4. Recent contributions of cognitive psychology to the study of clinical decision making may also hold considerable promise for emergency room research (26). While a detailed discussion of information-processing theory, social judgment theory, and decision theory is beyond the scope of this review, all three experimental approaches now appear to offer potentially valuable perspectives on collection and analysis of emergency room data.

In summary, research on emergency room decision making has experienced a renewed surge of interest as multivariate designs more accurately assess the reali-

ties of emergency evaluation. Existing and past research is now being tied to these more complex and powerful investigations in an effort to design more clinically and fiscally rational emergency programs. Future research needs to couple more accurate data collection with a multivariate approach that embraces a more comprehensive set of proven and reliable variables in key areas and a much broader range of available dispositions.

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The Heterogeneity of Schizoaffective Disorder: Implications for Treatment

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Until the 1970s, schizophrenia tended to be broadly defined in the United States, and the diagnosis subsumed patients who had affective as well as schizophrenic symptoms. With the introduction of lithium, however, manic-depressive illness became susceptible to treatment and gained attractiveness as a diagnosis. The ambiguous position of patients with schizoaffective disorder became clear. Cross-sectionally they were seen to resemble schizophrenic patients, but longitudinally they were more akin to patients with affective disorder. Numerous studies have attempted to establish that they are diagnostically distinct, but without clear results. The authors suggest that schizoaffective disorder is heterogeneous and that its treatment should be determined by specific indices as to its subtype.

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In recent years there has been a sharpening of interest in the differential diagnosis of psychotic disorders. The introduction of lithium to the United States in the early 1970s rekindled interest in the diagnosis of manic-depressive illness (1, 2) and helped to reverse a longstanding trend in American psychiatry to broaden the diagnosis of schizophrenia. This has stranded atypical psychotic patients, variously diagnosed as remitting or good-prognosis schizophrenic or schizoaffective, in controversy. As Kety noted in a review of schizophrenia research, "Schizophrenia and manic-depressive illness did not suffice to describe all psychotic patients in whom an organic basis was not apparent, and other designations were developed for these atypical psychoses (3)." In particular, it has long been recognized that some psychotic patients evince both schizophrenic and affective symptoms; and these patients' illnesses tend to have an acute onset, to be associated with good premorbid functioning, and to remit (4). Diagnostically, where do these schizoaffective patients fit in? Is their illness a variant of schizophrenia or affective illness or a heterogeneous mixture of disorders?

Two additional views of schizoaffective disorder have been suggested in the literature: first, that it is genetically distinct; and second, that it lies on a continuum between schizophrenia and affective disorders. Both of these views challenge the exclusiveness of Kraepelin's two-entity principle, whereby all psychotic disorders fall into one of two broad diagnostic categories—schizophrenia or manic-depressive illness. In the first case, if schizoaffective disorder is genetically distinct, this might argue in favor of a three-entity principle; in the second case, the idea of the continuum, theoretically there might be a great number of disorders not easily subsumed under a few broad clinical categories. At present, these theories are of little practical use to a clinician faced with the question of treatment. Given the psychopharmacologic remedies at our disposal, the Kraepelinian model for psychotic disorders, or the modified two-entity principle, is more attractive.

In this paper we shall trace the development of some of the major views of schizoaffective disorder and, using the heterogeneous model of schizoaffective disorder, discuss the implications for psychopharmacologic treatment.

PROGNOSTIC STUDIES: SCHIZOAFFECTIVE DISORDER VIEWED AS A SUBTYPE OF SCHIZOPHRENIA

In a review of the concept of schizophrenia, Pope (5) pointed out that one of the key features used by Kraepelin to distinguish dementia praecox from manic-depressive illness was the course of illness. Manic-depressive patients characteristically experienced exacerbations and remissions; dementia praecox patients tended to show a chronic course, with deterioration. Kety (3) noted that although Bleuler may have broadened the definition of schizophrenia by including latent forms of the illness, he too believed schizophrenia to be an essentially chronic disease which "can stop or retrograde at any stage, but does not permit a full *restutio ad integrum*." Thus, historically, those patients who seemed to meet the cardinal Bleulerian criteria for

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schizophrenia (the four A's), and particularly those who met his accessory criteria such as hallucinations and delusions, but who yet remitted entirely, have always eluded clear diagnosis.

Kasanin (6), in the 1930s, first employed the designation "the acute schizoaffective psychoses" and applied it to a group of patients whom he reported. He described this type of psychosis as "characterized by a very sudden onset in a setting of marked emotional turmoil with a distortion of the outside world and presence of false sensory impressions in some cases. The psychosis lasts a few weeks to a few months and is followed by a recovery." Later, Vaillant was among the first who, in the 1960s, became interested in systematically studying this group of patients, that is, schizophrenic patients who recovered. By "recovery," Vaillant meant "complete remission of symptoms and resumption of highest level of prior achievement" (7) and not that the patient could never relapse. In reviewing the work of earlier investigators who had similarly struggled with the relationship between remitting and nonremitting schizophrenia, Vaillant (8) saw that Langfeldt and Kant had independently arrived at common features which appeared to distinguish the two forms of illness. These factors were acute onset, confusion, depressive heredity, absence of schizoid premorbid adjustment, depression ("affective symptoms" is closer to Vaillant's actual description), and precipitating factors. For his own prospective study in 1964 (9), Vaillant selected these six prognostic criteria, in addition to a seventh, concern with death, all of which had proven statistically significant in discriminating between recovered schizophrenic patients and a control group of nonrecovered schizophrenic patients (9). It is noteworthy that four of his predictive factors (depressive heredity, acute onset, nonschizoid premorbid adjustment, and precipitants) were independent of the patient's cross-sectional symptoms but rather reflected longitudinal variables. On the basis of these factors, Vaillant was then able to predict remission versus nonremission in 82% of the cases.

Similar studies were conducted by Stephens et al. (10). They studied two groups of 50 patients diagnosed as schizophrenic at the Phipps Institute in the 1950s and 1960s; one group had the poorest outcome and the other had complete remission. Eleven factors differentiated the two groups in a statistically significant manner; five of these were also significant in Vaillant's work. (Two of Vaillant's factors, depressive heredity and concern with death, were found to be nonsignificant). Stephens et al., too, were then able to predict which patients would remit and which would deteriorate in about 80% of the cases. Their prognostic factors included marital status: married; good premorbid history (with respect to social adjustment and work history, which is slightly different from Vaillant's nonschizoid premorbid history); guilt; no low IQ; no emotional blunting; and no schizophrenic heredity. These additional good-prognosis factors again suggest, as also maintained by Stephens et al., the importance of longitudinal as well as cross-sectional factors in determining prognosis.

Vaillant's and Stephens et al.'s work makes clear that one can define a subpopulation of "schizophrenic" patients who have a better prognosis than typical Kraepelinian schizophrenic patients. In addition, one can, with approximately 80% certainty, combine a limited number of good prognostic factors and predict which patients will remit and which will deteriorate.

Pertinent to the issue of schizoaffective illness, among these positive predictors are affective symptoms or affective heredity. Some later authors have argued that a given proportion of these patients have a variant of affective disorder. But these original authors, at least as reflected in their writings in the 1960s and as implied by their use of the label "remitting schizophrenia," did not think so.

A REVERSAL IN THINKING ABOUT PSYCHOTIC DISORDERS: THE NONSPECIFICITY OF "SCHIZOPHRENIC" SYMPTOMS

A major conceptual shift occurred in American psychiatry in the 1970s, and it was one to which the work by Vaillant and Stephens et al. very much contributed. It was seen that cross-sectional symptoms alone were not specific either prognostically, in terms of predicting remission as they had demonstrated, or diagnostically, as other authors had asserted. Greater weight was given to longitudinal factors. This tended to broaden the concept of affective disorder, while narrowing the concept of schizophrenia.

In a 1978 article Pope and Lipinski (11) reviewed this quite fundamental shift in thinking about psychotic patients. They described the tendency of earlier American psychiatrists to rely heavily on cross-sectional "schizophrenic" symptoms in order to establish a diagnosis and noted that the influence of Bleuler and Schneider was to shift the focus of differential diagnosis between affective disorders and schizophrenia onto symptoms, as opposed to Kraepelin's emphasis on course. They pointed out that Bleuler introduced the ideas that schizophrenia had primary and secondary symptoms which characterized it and that Schneider described 11 first-rank symptoms of schizophrenia, writing that "when any of these modes of experience is undeniably present, and no somatic illness can be found, we may make the decisive clinical diagnosis of schizophrenia (11)." Bleuler (cited in reference 3), in fact, questioned the specificity of his own secondary symptoms, especially hallucinations and delusions, writing that they "are partial phenomena of the most varied diseases. Their presence is often helpful in making the diagnosis of a psychosis, but not in diagnosing the presence of schizophrenia." Nevertheless, the result of considering Bleuler's or Schneider's symptoms as specific for schizophrenia was the overdiagnosis of schizophrenia (11).

Pope and Lipinski (11) offered the view that all these so-called "schizophrenic" symptoms are actually nonspecific; Pope wrote elsewhere (12) that delusions, hallucinations, Schneiderian first-rank symptoms, ideas of reference, and catatonic symptoms occur in 20% to 50% of patients with well-validated mania or depression. Two papers relevant to this subject deserve close attention; one was written by Carlson and Goodwin (13), the second by Carpenter et al. (14).

Carlson and Goodwin retrospectively studied the progression of symptoms over time during an acute manic episode in 20 bipolar patients for whom drug therapy was not instituted in earlier phases, thus allowing the full clinical picture to unfold. They described three stages that were based mainly on the predominant mood. Stage I was characterized by euphoria, stage II by anger and irritability, and stage III by severe panic. In the third and final stage, which they observed in 70% of their sample, they described typical schizophrenic symptoms including bizarre psychomotor activity, loosening of associations, and bizarre and idiosyncratic delusions. This third stage of mania clearly included many of the so-called "schizophrenic" symptoms and offers compelling evidence for their nonspecificity. Certainly one would be hard pressed to call all of the observed delusions mood-congruent.

Carlson and Goodwin also found no significant relationship between the severity of the acute manic episode and the follow-up level of functioning. However, they acknowledged that they could not assess whether the ultimate outcome of these patients would be chronic schizophrenia. This was because, as they noted, the average length of illness in their sample was only 14 years, and they cited Astrup's "atypical" cases in which chronic schizophrenia occurred anywhere from 1 to 52 years after psychiatric symptoms began.

In a 1973 paper, Carpenter et al. (14) reported on eight of the 11 Schneiderian first-rank symptoms, clearly defined, and concluded that although these symptoms were significantly more prevalent ($p < 0.005$) in schizophrenic patients (51%) than in affective patients (23%), they were not exclusive to schizophrenia. In fact, they were even found in a small percentage of patients with character disorders and neuroses. These authors also concluded that in a 2-year follow-up, no relationship was seen between the presence or absence of first-rank symptoms and outcome.

In a 1965 paper about mania, Clayton et al. (15) addressed the issue of the relative weighting of affective versus schizophrenic symptoms in the prognosis of manic patients. On the basis of a sample of 31 manic patients, they noted that a characteristic triad of euphoria, overactivity, and push of speech was seen in almost all of their patients. They also noted that other symptoms such as confusion and a number of schizophrenic symptoms were seen as well. This group suggested that it is manic symptoms, such as the previously mentioned triad of symptoms, which may have diagnostic specificity for manic-depression, regardless of the presence of occasional schizophrenic symptoms. Parenthetically, we might note, as did they, that for this to be so there should also be a period of good functioning, which, in fact, was essentially a criterion for admission into their study (15).

One last symptom that Pope and Lipinski (11) and Abrams and Taylor (16) have suggested may similarly have diagnostic specificity for schizophrenia is flat affect. The problems with this symptom, however, are that it can be hard to distinguish from depressed affect and it may be due to a side effect of neuroleptics.

In summary, it is this reversal in thinking about psychotic disorders—that is, that schizophrenic symptoms are nonspecific but that affective symptoms such as the manic triad may have some diagnostic specificity—which sets the stage for thinking about many schizoaffective patients as having variants of affective illness.

SCHIZOAFFECTIVE DISORDER VIEWED AS A SUBTYPE OF AFFECTIVE ILLNESS

The Pope et al. group (17) from McLean Hospital studied three groups of patients: one group of schizoaffective patients who displayed a defined combination of affective and "schizophrenic" symptoms and two narrowly defined reference groups of patients with "definite" schizophrenia and/or "definite" manic-depressive disorder. The study group of schizoaffective patients was then compared with the two reference groups on three validating criteria: family history, short-term treatment response, and long-term outcome 1½ to 5 years after discharge.

Because of the kinds of patients on the research ward, Pope et al.'s study sample was actually composed of patients who met the Research Diagnostic Criteria (RDC) (18) for schizoaffective disorder, manic type. These criteria call for a full affective syndrome, either manic or depressive; either psychotic features during euthymia or mood-incongruent psychotic features; a minimum duration of signs of the illness of at least 1 week; and some degree of temporal overlapping of the affective syndrome with an active period of schizophrenic-like symptoms.

Pope et al. also looked at a more refined sample of schizoaffective manic phase patients, with two or more of the "schizophrenic symptoms" listed by the RDC, not with just one such symptom, as is required by the RDC. Comparing the one-symptom patients with manic and schizophrenic patients, they found that in terms of the validating criterion of family history, schizoaffective, manic type, patients were indistinguishable from manic patients but were significantly different from schizophrenic patients. Comparison of two-symptom patients with manic and schizophrenic patients on the same validating criterion of family history yielded similar results. Similarly, with respect to

both short-term therapy response and long-term follow-up, schizoaffective disorder, manic type, was significantly different from schizophrenia and similar to mania. Pope et al. concluded that schizoaffective disorder, manic type, should not be considered an independent diagnosis but rather should be subsumed under manic disorder (17).

Two other groups that compared mania with RDC-defined schizoaffective disorder, manic type, drew similar conclusions. A study by Abrams and Taylor (19), comparing 78 manic and 10 schizoaffective, manic subtype, patients, found that the two groups were not statistically different on a variety of validating criteria, which included clinical psychopathological variables, demographic variables, individual and family history features, and treatment response. Rosenthal et al. (20) found that in a bipolar I patient population, some of whom met the RDC for schizoaffective disorder and some of whom did not, the two groups did not differ significantly on most variables.

However, a recent article by Maj (21) disputes this finding. He divided his schizoaffective patients by polarity and also defined schizoaffective disorder according to the RDC. Maj compared the percentage of schizomanic and schizodepressive patients with first-degree relatives who had major affective disorders, schizoaffective disorder, and chronic schizophrenia with such percentages for "pure" manic and "pure" depressive patients. Although he did not find significant differences, he concluded that the family history patterns were "far from being similar" (21). Other differences in course and outcome in schizomanic and "pure" manic patients and in schizodepressive and "pure" depressive patients were seen.

There are two possible explanations for the differences in these findings. The first one is methodological. In none of these reports did the family history data collection technique actually involve interviews with all first-degree relatives, and thus the research was incomplete. A second explanation, as pointed out by Maj (21) and Maj and Perris (22), is that relying on a cross-sectional diagnosis of schizoaffective patients alone can result in a very heterogeneous group of patients. Although all the patients in the above four reports cross-sectionally fulfill the RDC for schizoaffective disorder, the longitudinal variables of these groups may have varied, leading to different results. As pointed out in a recent review of schizoaffective mania by Levinson and Levitt (23), the RDC for schizoaffective disorders have cross-sectional criteria that apply to a specific acute episode but also subtype along two dimensions—first, manic versus depressed and second, mainly affective versus mainly schizophrenic (or other)—and provide additional criteria for acute, subacute, subchronic, and chronic presentations. By mixing RDC subtypes and not including longitudinal course criteria, one can obtain quite heterogeneous samples.

SCHIZOAFFECTIVE ILLNESS VIEWED AS A HETEROGENEOUS COLLECTION OF DISORDERS

It might be true that schizoaffective illness is composed of a heterogeneous mixture of disorders. Authors who have supported this view include Fowler (24), Mendlewicz (25), Mendlewicz et al. (26), Baron et al. (27), Tsuang et al. (28), and Clayton (29).

A clear summary of this outlook has been presented by Fowler (24), who believes that mania, depression, and schizophrenia account for most cases of schizoaffective disorder. He relied on some older family history studies to compare schizoaffective disorder, or what he called good-prognosis schizophrenic, with poor-prognosis schizophrenia. Despite some conceded methodological problems in these studies, he summarized them to show that there is greater loading for affective disorders in the families of good-prognosis schizophrenic patients and greater loading for schizophrenia in the poor-prognosis group. This led him to ask whether good-prognosis schizophrenia is simply a variant of affective illness. But citing three studies carried out at Washington University (30–32 which made a concerted effort to interview first-degree relatives, Fowler (24) pointed out that the risk of affective disorder in first-degree relatives is significantly greater for manic patients (35%) than for good-prognosis schizophrenic patients (20%; $p<0.05$) or for unipolar depressive patients (16%; $p<0.001$). In addition, there was significantly more schizophrenia in first-degree relatives of good-prognosis schizophrenic patients (6%) than in first-degree relatives of manic patients (<1%; $p<0.01$) or of unipolar depressive patients (<1%; $p<0.001$).

Fowler (24) concluded that despite the similarity of familial affective disorder in good-prognosis schizophrenia and unipolar depression, because familial schizophrenia was more frequent in good-prognosis schizophrenia than in either mania or unipolar depression, his data were incompatible with the conclusion that good-prognosis schizophrenia was simply a variant of affective disorder. He further concluded that these data were consistent with the hypothesis that schizoaffective disorder is a heterogeneous mixture of disorders principally composed of mania, depression, and typical schizophrenia. (The diagnostic criteria for good-prognosis schizophrenia were those of McCabe et al. [30] and included acute onset with good premorbid psychosocial adjustment and remission between intervals. Affective symptoms were not required, yet their presence did not exclude patients from the sample. The diagnostic criteria for the other disorders were essentially those of Feighner et al. [33].) These criteria emphasize good prognosis more so than the mixing together of schizophrenic and affective symptoms, which is central to the RDC and later criteria for schizoaffective disorder. This might help explain some of the discrepancy between these family history findings and those reported by such authors as Pope et al. (17), Abrams and Taylor (19), and Rosenthal et al. (20).

Another author convinced of schizoaffective disorder's heterogeneity is Mendlewicz (25), who cited the heterogeneous response to lithium in schizoaffective patients (whom he considered atypical manic patients, but of whom he required at least one schizophrenic episode that was not concurrent with an affective syndrome). He compared family history profiles of schizoaffective patients with those of bipolar, unipolar, and schizophrenic patients. Like Fowler, he found high loading for affective illness in first-degree relatives of schizoaffective patients, close to that seen in bipolar patients, but he also found a higher than expected rate of schizophrenia (25). A later study of a somewhat expanded sample of patients produced similar results (26). Baron et al. (27) presented family history data that also corroborated this hypothesis.

As noted by Fowler (24) and others, at least two explanations other than heterogeneity should be considered. First, schizoaffective disorder could be on a continuum between affective disorder and schizophrenia. Second, schizoaffective disorder might in itself represent a disorder distinct from schizophrenia and affective illness. Brockington and Leff (34) presented some arguments compatible with a continuum or hierarchical model of psychosis, as opposed to the dichotomy model. They noted that the concordance of definitions of psychotic syndromes from different parts of the world can help choose between these two models. In mania, high concordance supports the idea that the manic syndrome is a discrete clinical entity. But in schizophrenia, where concordance is not so high, the homogeneity of the syndrome is less likely (34, 35). And in schizoaffective disorder, very low concordance suggests that "schizoaffective" does not describe any discrete population. Among the eight different definitions of schizoaffective disorder that they studied, concordance was very low (34).

An argument against the continuum model for psychoses, however, is that schizophrenia and affective disorder themselves tend to breed true and hence can be conceived of as distinct illnesses. Tsuang et al. (28, 36) addressed this issue and reviewed the subject in a study (36). The familial risk of schizophrenia in schizophrenic probands (3.2%) was much higher than that in manic (1.0%), depressed (0.9%), or surgical control probands (0.6%). The difference was significant for depressed and control probands and nonsignificant for manic probands. Similarly, the familial risk for affective disorder in manic (13.1%) and depressed (12.9%) patients was significantly greater than that in schizophrenic patients (7.0%). The familial risk for affective disorder was significantly greater in depressed patients (12.9%) than in surgical control subjects (7.6%) and nonsignificantly greater in manic patients (13.1%) than in surgical control subjects (7.6%). Thus schizophrenia and affective disorder, at least as defined by Feighner et al. (33) and Morrison et al. (37), seem not to overlap.

The theory that schizoaffective disorder represents an illness distinct from both affective disorder and schizophrenia is not supported by American family investigations (24), which show that typical schizophrenia and typical affective disorders are found in the first-degree relatives of schizoaffective patients. If the theory were correct, only schizoaffective disorders would be expected. Fowler did caution that in only one study of which he was aware, that of McCabe et al. (30), were the relatives of good-prognosis schizophrenic patients personally interviewed, and so these data may not be sound.

Still, a more recent review by Abrams (38) of a selected number of studies that examined, among other things, the family history profiles of schizoaffective probands, showed no evidence that schizoaffective disorder is a distinct genetic entity. Three of five of these studies, discussed briefly below, did make efforts to interview relatives directly. Mendlewicz et al. (26) found only rare instances of schizoaffective illness in the relatives of schizoaffective probands. Baron et al. (27) found other diagnoses, especially affective ones, more commonly than schizoaffective illness in the relatives of schizoaffective patients. These patients were defined as acute or subacute according to the RDC. Only the study by Gershon et al. (39) found schizoaffective probands to have more schizoaffective relatives than other proband groups. But these probands had more relatives with other mental illness as well. Gershon et al. studied predominantly affective schizoaffective patients. A problem in all these studies is that a diagnosis of schizoaffective disorder is not easy to make retrospectively and thus may be underrepresented (29).

SCHIZOAFFECTIVE DISORDER: STRATEGIES OF SUBDIVISION

Given the picture of schizoaffective disorder as possibly representing a heterogeneous sample, the research strategy to subdivide it into more homogeneous subtypes has been advocated. Efforts to subdivide schizoaffective disorder by symptom presentation have tended to undermine a simple, two-subtype model. Maj and Perris (22) suggested that the presence of a full manic syndrome may be more significant prognostically in schizoaffective patients than a full depressive syndrome. Kendell (40) has also emphasized the importance of dividing schizoaffective disorder by polarity. Given his group's definitions of schizomania and schizodepression, their findings suggest that schizomania resembles affective psychoses much more closely than it resembles schizophrenia, whereas schizodepression's relationship to schizophrenia is much more prominent. Similarly, Angst has recently stressed the importance of dividing schizoaffective disorder by polarity in future research on the illness's course (41).

Such a division has been performed by Williams and McGlashan (42, 43) in a study that defined schizoaffective disorder very rigorously, requiring the presence of full *DSM-III* affective disorder and schizophren-

ic syndromes. Three subtypes were defined: manic, bipolar, and depressive. No significant differences with regard to long-term outcome were seen among these groups, which seemed longitudinally most similar to schizophrenic patients. The authors noted that they may have selected a chronic sample; although outcome differences were not significant, the depressive subgroup did obtain better results.

Two further efforts to subdivide schizoaffective disorder are those of Tsuang et al. (28) and Clayton (29). Tsuang et al. have advocated schizophrenic, affective, and undifferentiated subtypes based upon an analysis of demographic, clinical, and longitudinal features. They have proposed preliminary research and clinical diagnostic criteria for schizoaffective disorder that are based upon this subtyping. Clayton has emphasized the importance of dividing schizoaffective disorder by polarity into a manic phase and a depressed phase; the Spitzer et al. RDC (18) agree.

Another form of subtyping schizoaffective disorder has been to divide it into a consecutive versus a concurrent form, labeled type I and type II by Maj and Perris (22). In the consecutive form, affective and schizophrenic episodes occur sequentially. For example, one subtype begins as a schizophrenic syndrome and later becomes a recurrent affective syndrome, while a second subtype begins as an affective syndrome and later develops into a deteriorating schizophrenic syndrome.

In the *DSM-III-R* criteria for schizoaffective disorder, the idea of specifying bipolar or depressive subtypes is advocated. The criteria for schizoaffective disorder include the requirement, at some time during the illness, for either a major depressive or manic syndrome concurrent with active-phase symptoms of schizophrenia. In addition, delusions or hallucinations for at least 2 weeks, during the absence of prominent affective symptoms (i.e., psychosis during euthymia), must occur during an episode of the illness. Finally, schizophrenia should be ruled out, i.e., the mood syndrome should not be brief relative to the total duration of the psychosis, as should an organic factor. The implications of *DSM-III-R* criteria are not straightforward. The criteria do not subtype along schizophrenic and affective poles with the aid of longitudinal or course features except, perhaps, for their criterion calling for a period of psychosis together with relative euthymia. This criterion may select for a more schizophrenic subtype of the disorder. The criterion calling for a full affective syndrome (i.e., a major depressive or manic syndrome) concurrent with active-phase symptoms of schizophrenia, which may fall short of a full schizophrenic syndrome, conversely, may select for a more affective subtype of the disorder. Hence, it is our suspicion that schizoaffective patients selected with *DSM-III-R* criteria will still represent a heterogeneous sample.

A remaining problem in subtyping patients who do not straightforwardly fit either affective or schizophrenic categories is the mixing-in of other atypical psychoses, such as the cycloid psychoses described by Perris (44), the reactive (psychogenic) psychoses of Stromgren (45), or the *bouffées délirantes* described by Pichot (46). In fact, if the continuum hypothesis of psychoses is most accurate, there could be an infinite variety of psychoses. The symptomatic schizophrenias, such as amphetamine- or alcohol-induced psychoses or those associated with seizures, might add heterogeneity as well, although, ideally, these might be screened out through appropriate laboratory tests.

As will be revealed in the next section on the clinical treatment of schizoaffective disorder, it is our belief that subtyping of schizoaffective patients is indeed useful, particularly so for the purpose of psychopharmacologic intervention.

TREATMENT IMPLICATIONS OF VIEWING SCHIZOAFFECTIVE DISORDER AS HETEROGENEOUS

Treatment studies of schizoaffective disorder are plagued by an absence of uniformity in defining the disorder. As mentioned earlier, Brockington and Leff (34) found that the mean concordance for eight definitions of schizoaffective disorder was very low. It has been pointed out by Tsuang and Marneros (47) that one weakness in Brockington and Leff's study was the elimination of any longitudinal criteria, so that cross-sectional criteria could not be expected to correlate well. Nonetheless, Brockington and Leff's point applies well to the literature in general, which often relies on essentially cross-sectional features to define schizoaffective disorder and makes the interpretation of treatment studies so difficult.

The division of schizoaffective disorders by polarity is particularly relevant, in our opinion, to treatment. As Clayton (29) has maintained, a number of family history studies, including her own collaborative study as well as other studies (17, 19, 20, 39), support this distinction. But family data from two other studies that Clayton also cited, one by Cadoret et al. (48) and one by Angst et al. (49), do not add support to this distinction by polarity.

Methodological problems with existing studies need to be addressed by further research. One criticism of the conception of schizoaffective disorder is that it works only from a cross-sectional vantage point. From a longitudinal perspective it has been reported that many schizoaffective psychoses change types in what has been referred to as a polymorphous course (50, 51). Clayton's own opinion (29) is that schizoaffective mania resembles bipolar affective disorder, perhaps in a more severe form, with the proviso that some of these patients are probably excited schizophrenic patients. Her opinion of schizoaffective depression is that it represents a diverse group of disorders.

TREATMENT STUDIES OF SCHIZOMANIC PATIENTS

To the extent that the above hypothesis that a certain proportion of schizomanic patients resemble bipolar patients has validity, the use of lithium for these patients seems indicated. Pope et al. (17) and Abrams and Taylor (19) saw their schizomanic patients respond to a variety of medications, including lithium alone, neuroleptics alone, lithium and neuroleptics, and ECT, much as manic patients did. Brockington et al. (52) compared the treatment response of a small sample of schizomanic patients to a 1-month trial with chlorpromazine versus lithium. Although the numbers were too small to permit definite conclusions, lithium and chlorpromazine appeared equally effective. Interestingly, lithium appeared as effective as chlorpromazine in its effects on both manic and schizophrenic symptoms. The contention that lithium improves only the affective component of schizoaffective disorder (a controversy reviewed in an article by Delva and Letemendia [53]) was not supported by the Brockington group.

Combination drug treatment in schizoaffective patients often occurs. At times, it is clinically difficult to taper and/or stop an antipsychotic in these patients after initially starting treatment with lithium and an antipsychotic. A study which specifically addressed the combined use of lithium carbonate and haloperidol in patients with RDC-defined schizoaffective disorder, manic type, is that of Biederman et al. (54). They performed a 5-week study comparing the response of these patients to lithium carbonate and haloperidol versus placebo and haloperidol. Patients with schizophrenic and affective subtypes of schizoaffective disorder were included in their study.

Biederman et al. reported that the lithium carbonate plus haloperidol group improved significantly more than the placebo plus haloperidol group, although only modestly, as measured by mean scores by week 5 on the Brief Psychiatric Rating Scale. The overall improvement scores on two other scales also showed consistently more improvement in the lithium carbonate plus haloperidol group, but the differences on these scales were not significant. The modest benefit from the combination of lithium carbonate and a neuroleptic, such as haloperidol, must be weighed, then, against the risks of added toxicity.

Biederman et al. also addressed the issue of lithium specifically treating manic symptoms alone. They noted that their data were not supportive of the view that lithium improves only the affective component of mixed conditions. They also raised the point that an affective disturbance may secondarily cause cognitive symptoms and that lithium supplementation may be treating these. Two other groups that do not support the specificity of lithium for affective symptoms are Prien et al. (55) and Braden et al. (56). In the Prien et al. study, a sample of schizoaffective, excited state, patients were classified as highly active or mildly active on the basis of degree of hyperactivity shown at admission. In the highly active group lithium was not as effective as chlorpromazine, but with the mildly active group lithium was just as effective as chlorpromazine, and it improved both affective and schizophrenic symptoms. Braden et al. reported similar findings for a less homogeneous sample of psychotic inpatients, also divided into overactive and not overactive groups. Hence, in combination treatment of schizoaffective patients, when activity level can be controlled by neuroleptics, it is possible that lithium might work on both the affective and schizophrenic symptoms. Further investigation is required to clarify this issue.

Bigelow et al. (57), also dealing with the issue of combination therapy, presented a case history of a woman, hospitalized for approximately 40 years all together, whom they diagnosed by RDC as schizoaffective. The woman went through pronounced behavioral cycles with fluctuating activity levels, with chronic psychosis, and was refractory to substantial doses of a series of antipsychotics and antidepressants. A trial of lithium carbonate alone also produced no significant change. Maintenance ECT did result in considerable improvement until the treatments were stopped. The combination of lithium and acetaphenazine, however, resulted in remission. After a placebo substitution for lithium resulted in a typical reexacerbation, lithium was reinstituted, with apparent success. Bigelow et al. speculated about a possible therapeutic synergy between the two drugs. They pointed out that the impact of the combined treatment did not become clearly apparent until after about 6 months, or four behavior cycles, and stated that it may be important to sustain such prolonged trials in order to obtain similar results.

Carman et al. (58) also argued for the potential advantages of combining lithium and neuroleptics in the treatment of schizoaffective and schizophrenic patients. They noted that affective symptoms and/or an episodic course appeared to favor a positive response to such a treatment regimen. They added, however, that several patients without affective symptoms or an episodic course also responded.

Two other studies, by Small et al. (59) and Growe et al. (60), also reported some positive responses in mixed populations of schizophrenic and schizoaffective patients to combination treatment with lithium and neuroleptics. Small et al. subtyped their patients according to the Feighner et al. (33) and Tsuang and Winokur (61) criteria. They found that schizomanic patients, as one might expect, had a good response to the combination treatment but that schizodepressive and psychotic patients from other categories had a less predictable response, although some were nonetheless potential responders as well. Growe et al. noted that their results were consistent with anecdotal reports that lithium affects activity levels but not the primary symptoms of schizophrenia.

The combination of lithium and neuroleptics raises other issues. First, there is a possibility of a lower rate of tardive dyskinesia. Delayed supersensitivity of do-

pamine receptors when lithium was added to a neuroleptic has been shown in animal studies (62). Second, there is also the possibility of added toxicity with the combination of drugs. However, a recent retrospective study of manic patients by Goldney and Spence (63) seemed to show that the combination of neuroleptic drugs, particularly haloperidol, with lithium was no more toxic than neuroleptics alone. Lastly, there may be greater vulnerability to neurotoxicity in schizophrenic patients taking lithium, a subject reviewed elsewhere (53). In an article by Shopsin et al. (64), six of 11 acute schizophrenic patients treated with lithium carbonate reportedly developed "symptoms of a toxic-confusional state," even at moderate to low serum levels.

Alexander et al. (65), in contrast to the Shopsin et al. group, did not find lithium neurotoxicity in 13 patients who met the RDC for schizophrenia and schizoaffective illness. Citing a point made by Quitkin et al. (66), they suggested that the schizophrenic patients in the Shopsin et al. study might have been "asocial schizophrenics" with CNS dysfunction who were prone to toxicity with any psychotic agent. Prakash et al. (67) treated 20 schizophrenic patients with a combination of lithium and neuroleptics and observed neurotoxicity in four; the neurotoxicity was reversible within 2 days to within 1 month after lithium treatment was stopped. They, too, concluded, citing Alexander et al. (65) and Quitkin et al. (66), that the greater sensitivity to neurotoxicity of these schizophrenic patients may reflect CNS dysfunction. Thus, there may be a subgroup of schizophrenic patients with underlying CNS dysfunction who may, indeed, be more susceptible to lithium neurotoxicity.

Whether schizophrenic patients have a greater prevalence of CNS dysfunction than do bipolar patients is a question that at this point cannot be answered. There is, however, some post-mortem evidence of structural brain changes in schizophrenia that include lighter weight, larger lateral ventricles (particularly in the temporal horn), and thinner parahippocampal cortices than in the brains of patients with affective disorder (68). As recently reviewed by Goetz and van Kammen (69) and Andreasen (70), there is a group of schizophrenic patients with ventricle enlargement. Some data suggest basal ganglia (pallidum internum) and limbic system brain volume shrinkage in the limbic temporal structures of schizophrenic patients (71). If current hypotheses about brain abnormalities in schizophrenic patients prove true, they may help explain the greater vulnerability of these patients to lithium neurotoxicity.

TREATMENT STUDIES OF SCHIZODEPRESSIVE PATIENTS

Treatment of schizoaffective depressed patients is similarly complicated by the probable heterogeneity of this group. In Brockington et al.'s study (72) of an intentionally broadly defined sample of schizoaffective depressed patients, they noted that their sample appeared to have very few bipolar manic-depressive patients. They thus concluded that their study "mainly focused on the interface between schizophrenia and unipolar depressive psychosis." The implication of this is that one is most commonly treating either a schizophrenia-related depression or a delusional unipolar depression when one evaluates a schizodepressive patient. Brockington et al. did, however, find that a number of patients in this group had hypomanic features, usually following a major depressive illness. Thus, the possibility of bipolar illness in schizoaffective depressed-phase patients should not necessarily be excluded.

Siris et al. (73) noted that in 10 of 12 earlier studies on the addition of antidepressants to neuroleptics in schizophrenia, combining tricyclic antidepressants and neuroleptics was not statistically superior to treatment with phenothiazines alone. Two studies that separated out schizophrenic patients with depressive features were an exception to this trend; this subgroup of patients appeared to do better with a combination of a phenothiazine and a tricyclic antidepressant. Siris et al.'s review of data on the combination of monoamine oxidase inhibitors and neuroleptics does not really further clarify this murky area. Many of these studies were older studies, and hence, as pointed out elsewhere (74), only a small number used diagnostic criteria translatable into current practice. Siris et al. concluded that further research with patients representing more distinct diagnostic subcategories, and perhaps biological variables to help elucidate the occurrence of depression in schizophrenic patients, will be necessary to determine who among depressed schizophrenic patients might benefit from the use of antidepressant compounds.

In a more recent clinical trial by Prusoff et al. (75), in which a subgroup of ambulatory schizophrenic patients with a depressive syndrome was examined specifically to assess the impact of amitriptyline on ongoing treatment with perphenazine, results were mixed. The researchers advised caution in interpreting their results because only 35 patients were included in endpoint analyses. Nonetheless, they concluded that their study indicated some relief of symptoms of depression, particularly anxiety-depression, in ambulatory schizophrenic patients taking a combination of amitriptyline and perphenazine. Balanced against this, they reported an increase in thought disorder and an increase in blood pressure. They also presented data showing weight gain with the combination treatment, although no statistical significance was evident on the basis of the rather small sample size. It should be pointed out that the doses employed in that study were relatively low, equaling roughly 30 mg/day of perphenazine and roughly 110 to 130 mg/day of amitriptyline. Since no data on blood levels were offered, it is hard to know if the patients received adequate doses.

The interacting effects of blood levels on tricyclics and neuroleptics do further complicate the assessment

of combination therapy of schizodepressive patients. The above two studies did not control for tricyclic blood levels or for neuroleptic blood levels. In addition, the potential anticholinergic effects of tricyclics on patients taking neuroleptics might give an appearance of improvement of depression. For example, bradykinesia, appearing as psychomotor retardation, might be reduced; and the subjective feeling of improvement might also be experienced through reduction of discomfort from akathisia. Further work needs to be done to separate the effects of these drugs.

Separate investigations have addressed the treatment of delusional depression. Ideally, patients with delusional depression are depressed with psychotic features, rather than schizophrenic with depressive features. In a recent article Spiker et al. (76) compared the treatment of delusional depression with amitriptyline alone, perphenazine alone, and a combination of the two. That study was a prospective, double-blind study. The patients were defined by the RDC as having a definite diagnosis of major depressive disorder, psychotic subtype. The results showed that the combination of amitriptyline and perphenazine was clearly superior ($p<0.01$). Fourteen of 18 (78%) of the patients treated with this combination were considered responders, whereas only seven of 17 (41%) who received amitriptyline alone and three of 16 (19%) treated with perphenazine alone were considered responders. For comparison, a rough estimate of response rate to ECT in patients with delusional depression can be found in a retrospective chart study by Perry et al. (77). They looked at patients who met the *DSM-III* criteria for major depression with psychotic features and found that 86% of 14 ECT-treated patients had a favorable treatment response.

As Spiker et al. relied on the RDC for their sample, by definition mood-incongruent delusions and hallucinations or delusions suggestive of schizoaffective disorder, such as delusions during euthymia, were excluded; thus, their population probably represented the healthier pole of the spectrum of schizodepressive patients. For example, Brockington et al. (52), using amitriptyline alone, chlorpromazine alone, and a combination of the two, found a generally poorer response to drugs among broadly defined schizodepressive patients. Nonetheless, the idea of combined treatment seems relevant, indeed, to the treatment of schizodepressive patients. Notably, Spiker et al. asserted that their better results were not simply a reflection of increased amitriptyline plus nortriptyline blood levels, which do occur with concomitant therapy with phenothiazines.

A final point which Spiker et al. addressed is that although amitriptyline was less effective than the combination of amitriptyline and perphenazine, amitriptyline alone was indeed an effective treatment for some patients. In light of the 41% response rate with amitriptyline alone, a conservative drug approach might be to precede combination treatment with a trial of an antidepressant alone, depending upon the severity of the psychosis, especially if the patient is in a controlled setting such as a hospital. None of the amitriptyline nonresponders became more psychotic than they had been at the outset.

Another combination treatment approach that has been tried with delusional depression is lithium augmentation of combined neuroleptic-tricyclic treatment (78, 79). This is an outgrowth of reports (80, 81) regarding lithium augmentation of antidepressant therapy in treatment-refractory depressive patients. In a recent study, Nelson and Mazure (78) retrospectively compared responses of such patients to various treatments. The patients met *DSM-III* criteria for major depression with mood-congruent psychotic features (delusional). All had proven refractory to antipsychotic-antidepressant treatment. They were divided into unipolar or bipolar groups, with delusional or psychotic depression. Some were treated with ECT and some with lithium. The patients who received ECT were all reportedly unipolar delusional depressive patients, whereas those who received lithium augmentation were a mixture of unipolar and bipolar type I and type II delusional depressed patients. These authors concluded that in patients with bipolar psychotic depression who did not respond to the combination of an antipsychotic and an antidepressant, augmentation with lithium was an effective treatment. However, lithium augmentation was not as effective in unipolar patients. For that group, the authors asserted, ECT appeared to be a superior form of treatment. They noted the need for a prospective study to further clarify the role of lithium augmentation.

A final standard treatment modality that may be indicated with schizoaffective patients is ECT, and intuitively this modality, although not exclusively appropriate for schizodepressed (versus schizomanic) patients, seems most specifically appropriate for them. In a 30- to 40-year follow-up of schizoaffective patients not divided by polarity, Tsuang et al. (82) presented interesting information on mortality. The group of patients who had at some time between admission and follow-up received ECT had a statistically significant lower mortality than the group who had not. Tsuang et al. noted that the two groups of patients were not significantly different in sex distribution or age at admission. All of the suicides ($N=3$) were found in the non-ECT group. This last difference was not, however, statistically significant. The authors concluded that although the true nature of schizoaffective disorder is as yet not known, ECT may benefit schizoaffective patients by lowering their mortality and suicide risk.

New forms of treatment may have a role in schizoaffective disorder. Carbamazepine, for example, has been promoted as effective in treating manic-depressive illness, particularly the manic phase, in bipolar patients unresponsive to lithium (83) and in other psychotic (84) and nonpsychotic conditions (85). The combination of neuroleptics and carbamazepine has also been examined (84). Other agents that are also being investigated for schizophrenia (74), and that

may or may not have an application for schizoaffective disorder, include propranolol, the benzodiazepines, and clonidine. These newer medicines await further research.

CONCLUSIONS

In conclusion, we have attempted to outline the history of how the complex syndrome of schizoaffective illness has been viewed by various authors. Five major views of schizoaffective disorder have been considered: that it is a variant of schizophrenia, a variant of affective disorder, a heterogeneous mixture of disorders, a distinct disorder, or a midpoint on a continuum between schizophrenia and affective disorder. Taking the position that schizoaffective disorder is heterogeneous, we have reviewed the pharmacological treatment implications.

Until there is greater agreement on the criteria for and the meaning of schizoaffective disorder, reports on treatment results will not be generalizable. Firm recommendations for treatment, then, are at this point premature. As a general principle, it makes sense to divide schizoaffective patients by polarity and then consider the previously discussed issues. These include the possible role of lithium, an antidepressant, or various combination treatments, for example, lithium and antipsychotics or antidepressants and antipsychotics, perhaps with lithium augmentation. Finally, ECT must also be considered. At this point, one must concede that the pharmacological treatment of these patients remains essentially empirical.

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PET Imaging of Cortical S_2 Serotonin Receptors After Stroke: Lateralized Changes and Relationship to Depression

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Patients with right-hemisphere strokes (N=9) more than 1 year after injury had greater cortical binding of (3-N-[^{11}C]methyl)spiperone than a similar group of patients with left-hemisphere strokes (N=8) or normal control subjects (N=17). The higher S_2 serotonin receptor binding occurred in uninjured regions of the right parietal and temporal cortex. The ratio of binding in the ipsilateral to contralateral cortex showed a significant negative correlation with severity of depression scores in the left temporal cortex. These findings suggest that the biochemical response of the brain may be different depending on which hemisphere is injured and that some depressions may be a consequence of the failure to upregulate serotonin receptors after stroke.

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Identification of specific structures responsible for behavioral symptoms that follow brain injury has been a major goal of clinical neuropsychiatric research (1, 2). As many early investigators recognized, however, the mechanisms by which brain lesions lead to clinical deficits may involve either direct damage to individual structures or the indirect disconnection of critically linked but distant sites (3, 4). Traditional clinical-pathological correlations, therefore, have provided only partial insight into the organization of neural systems involved in symptom production.

The difficulty in making these structure-function relationships is most apparent when evaluating psychiatric symptoms such as depression, apathy, or emotional lability that follow brain injury and has led some investigators to assume that they are a psychological response to associated physical deficits (5, 6). Studies of depression after stroke, however, have found that depression was significantly correlated with anterior brain injury but not with the severity of physical impairments (7–10). It has also been observed that these depressions are clinically responsive to antidepressant drugs that have prominent serotonergic effects (11).

Positron emission tomography (PET) can be used to measure neurotransmitter-receptor binding in vivo (12, 13). This technique provides an opportunity to examine neurochemical changes associated with specific brain lesions, as well as structures that are not directly injured but which may be important in the development of symptoms after stroke.

The present report describes cortical S_2 serotonin receptor binding measured with PET and its relationship to measures of depression, physical impairment, and cognitive function in patients with focal ischemic lesions of the right or left cerebral hemisphere.

METHOD

Subjects for this study were selected from patients participating in the Stroke Data Bank sponsored by the National Institute of Neurological and Communicative Disorders and Stroke. These patients had been initially admitted to the University of Maryland Hospital (14) for treatment of acute thromboembolic infarction or intracerebral hemorrhage. Patients were included if, after giving informed consent, they met the following criteria: 1) as demonstrated by either CT scan or carotid angiography, a focal lesion of either the right or left hemisphere; 2) absence of other neurologic, neurotoxic, or metabolic conditions; 3) absence of a significant verbal comprehension deficit; and 4) occurrence of stroke more than 4 months earlier, with a stable clinical neurological course.

Diagnostic neurological examinations were performed in the hospital and used criteria established by the Stroke Data Bank (14). Patients were administered a series of standardized, quantitative measures of mood (Present State Examination [PSE] [15], Hamilton Rating Scale for Depression [16], Zung Self-Rating Depression Scale [17]), cognitive function (Mini-Mental State examination [18]), and activities of daily living (Johns Hopkins Functional Inventory [19]) on the day of the PET scan. The neurological examination was repeated as well. In previous publications, we have shown that these instruments provide reliable and valid measurements in this stroke population (19, 20). A psychiatric diagnosis was established from symptoms elicited by the semistructured psychiatric interview of the PSE and by using *DSM-III* symptom criteria for major depression or depressive neurosis (dysthymic disorder) (20).

CT scans obtained during the acute hospitalization or in follow-up clinic visits were used to assess lesion size and location. Scans were read by one of us (H.S.M.), who was blind to the psychopathological findings. All studies were performed with the same scanner and an imaging plane parallel to the canthomeatal line. Lesion volume (expressed as a percent of total brain volume) was calculated from the ratio of the largest cross-sectional area of lesion on any CT scan slice to the cross-sectional area of the whole brain on the slice passing through the lateral ventricles. The anterior and posterior location of each lesion was defined as the mean distance of the anterior or posterior border of the lesion from the frontal pole (expressed as a percent of the overall anterior-posterior distance) averaged over all slices in which the lesion was visible. An additional CT scan was done to determine the precise imaging plane to be used for the PET study (12). Three images, corresponding to the slice separation of the Neuro ECAT scanner (3.2 cm), and which best localized the caudate-putamen complex, cerebellum, and frontal, temporal, and parietal cortex were selected. An alignment line was then drawn on a low-temperature thermoplastic mask (Polysplint, Poly-Med Manufacturing Co.) that had been contoured to the patient's face.

(3-N-[^{11}C]methyl)spiperone (NMSP) was synthesized at the Johns Hopkins Biomedical Tracer Center (21). A dose of approximately 15–20 mCi of NMSP (total mass=0.233±0.27 (1 SD) μg/kg, specific activity=1,000–2,000 Ci/mmol; no significant difference between patients and volunteers) was administered intravenously over 10–20 seconds, while the patients lay supine, with their heads positioned in the scanner. Studies were performed with the Neuro ECAT scanner operating in the high resolution mode (in-plane resolution of 1.6 cm at full width half maximum). Images were obtained over 90 minutes by using scan acquisition times of increasing duration (2–30 minutes).

Although NMSP binds irreversibly (little measurable dissociation during the 90-minute PET acquisition) to D_2 dopamine receptors in the caudate-putamen, reversible binding to predominantly S_2 receptors occurs in the cortex. Elaboration of the steady-state model for irreversible receptor binding ligands (13) has been applied to the reversible binding properties of this tracer in the cortex (22). By using plasma sampling (brain input function) and serial PET images (brain time-activity curve), it can be shown that equilibrium is reached about 20–30 minutes after injection. Thus, through examination of the latest time points (70–90 minutes), an equilibrium state between the plasma compartment, the free-brain and non-specifically bound compartment, and the receptor compartment (specifically bound) is probably assured (D.F. Wong, unpublished data). Images were first corrected for radioactive decay, followed by a calculated attenuation correction that used a fitted ellipse. The borders of the infarct were determined by matching the CT scan with the corresponding PET image obtained 0–6 minutes after injection. Because these early scans reflect mainly tracer delivery and are more sensitive to blood flow than later scans, they were used to estimate the maximum region of altered blood flow that might be expected in the affected hemisphere (13). A small, 4×5-pixel (1.5 cm^2) region of interest was then placed well within the estimated border of the lesion and in areas of uninvolved frontal, temporal, and parietal cortex in the ipsilateral hemisphere and in symmetrical areas on the contralateral side. A ratio of ipsilateral to contralateral activity was calculated for each region in the 70–90-minute scans. A normalized ratio of total to nonspecific cortical NMSP binding was also calculated for all right and left regions by dividing regional cortex activity by the average of the right and left cerebellar activity (22).

The asymmetry ratio in stroke patients was compared with that in an identically scanned group of 17 age-comparable normal volunteers (nine men, eight women; mean±SD age=47.1±12 years). These subjects had no history of psychiatric or neurological disease and had normal CT scans. Regions of interest from frontal, temporal, and parietal cortex were

TABLE 1. Demographic Characteristics of Patients With Left-Hemisphere or Right-Hemisphere Stroke

Characteristic	Left-Hemisphere Stroke (N=8)	Right-Hemisphere Stroke (N=9)
Sex		
Male	7	4
Female	1	5
Race		
Black	1	4
Caucasian	7	5
Marital Status		
Married	5	5
Single/widowed	2	1
Divorced/separated	1	3
Hollingshead (class IV or V)	5	9
Other medical illnesses (hypertension, diabetes, or heart disease)	4	7
Prior psychiatric illness	1	0
Smoking history (one pack or more/day)	4	6
Alcohol abuse	0	1
Medications		
Antihypertensives	5	4
Anticonvulsants	0	2
Minor tranquilizers	3	2
Lithium	1	0

TABLE 2. Neurologic and Radiographic Characteristics of Patients With Left-Hemisphere or Right-Hemisphere Stroke

Characteristic	Left-Hemisphere Stroke (N=8)	Right-Hemisphere Stroke (N=9)
Handedness		
Right	7	8
Left	1	1
Motor weakness	4	5
Sensory loss	3	4
Visual field deficit	3	4
Aphasia		
Anomic	1	0
Transcortical	1	0
Left hemi-neglect	0	1
Anosognosia	0	0
Spatial deficit	0	1
Brain stem signs	2	2
Ischemic infarct	7	8
Hemorrhage	1	1
Demonstrable lesion by CT scan	6	7
Demonstrable brain stem lesion by angiogram	2	2

sampled in a manner identical to that for the stroke patients.

Statistical analysis was done with means and standard deviations, analysis of variance, and Pearson correlation coefficients. Nonparametric data was analyzed with Mann-Whitney U tests and Spearman rank correlation coefficients. Frequency distributions were analyzed through chi-square tests with Yates' modification for expected cell sizes less than five.

RESULTS

The background characteristics of the stroke patients are shown in table 1. There were no statistically significant differences between the patients with left-hemisphere (N=8) and right-hemisphere (N=9) lesions. The mean ages of the two groups were 54.1±11 and 55.6±14 years, respectively, and they were evaluated and scanned 18±14 and 15±9 months after their presenting illness.

There were no statistically significant differences between patients with right- or left-hemisphere lesions in the frequency of motor or sensory impairments or in handedness (table 2). There were a small number of patients with either aphasic or nondominant hemisphere syndromes. One patient in each group had a hemorrhagic infarct.

There were no significant differences between patients with left- and right-hemisphere strokes in either lesion volume or lesion location. For patients with left-hemisphere strokes, anterior location was 33%±19% of the overall anterior-posterior distance, posterior location was 63%±22%, and lesion volume was 7.7%±5.2%. Corresponding data for patients with right-hemisphere stroke were 38%±16%, 61%±16%, and 4.1%±3.7%, respectively. Figure 1 illustrates the location of each patient's lesion by using the largest cross-sectional area of the stroke seen on the CT scans. There were no statistically significant differences between the right- and left-hemisphere groups with respect to subcortical involvement (two of eight in left hemisphere versus three of nine in the right hemisphere), dorsolateral cortical involvement (one of eight in left hemisphere versus 0 of nine in right hemisphere), or basotemporal cortical involvement (0 of eight in left hemisphere and two of nine in right hemisphere).

There were no significant differences between patients with left- and right-hemisphere lesions in activities of daily living or cognitive function (table 3). Of the 17 patients, four (one with left-hemisphere stroke and three with right-hemisphere stroke) met diagnostic criteria for major depression and one with left-hemisphere stroke met criteria for depressive neurosis, but there were no statistically significant differences between the left- and right-stroke patients in either the frequency of depression or mean depression scores (table 3).

Regional activity 70–90 minutes after injection (counts per pixel per millicurie of injected dose), measured within the stroke site, was significantly decreased in both the right- and left-hemisphere stroke groups compared to mirror regions in the contralateral (normal) hemisphere (mean±SD ratio of stroke to nonstroke regions: right-hemisphere strokes=0.677±

FIGURE 1. Stroke Lesion Templates for Patients With Left-Hemisphere (N=8) or Right-Hemisphere (N=9) Stroke

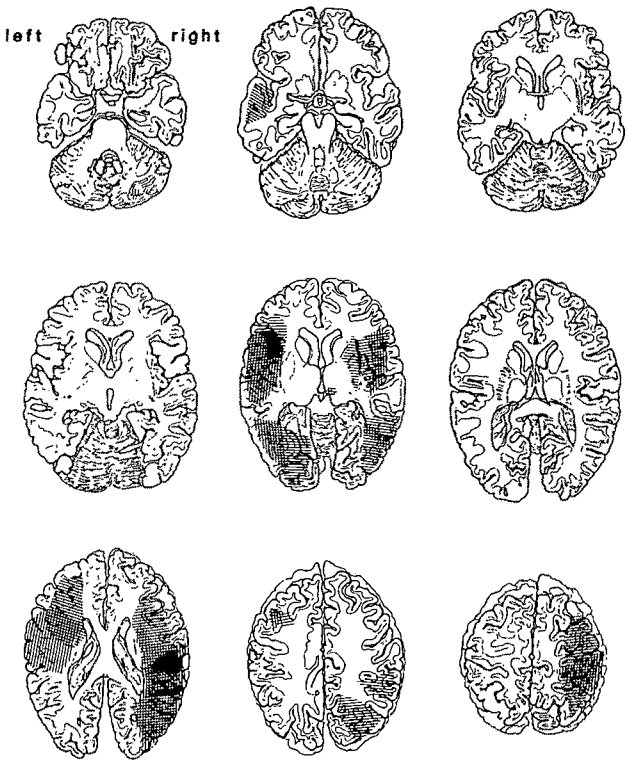


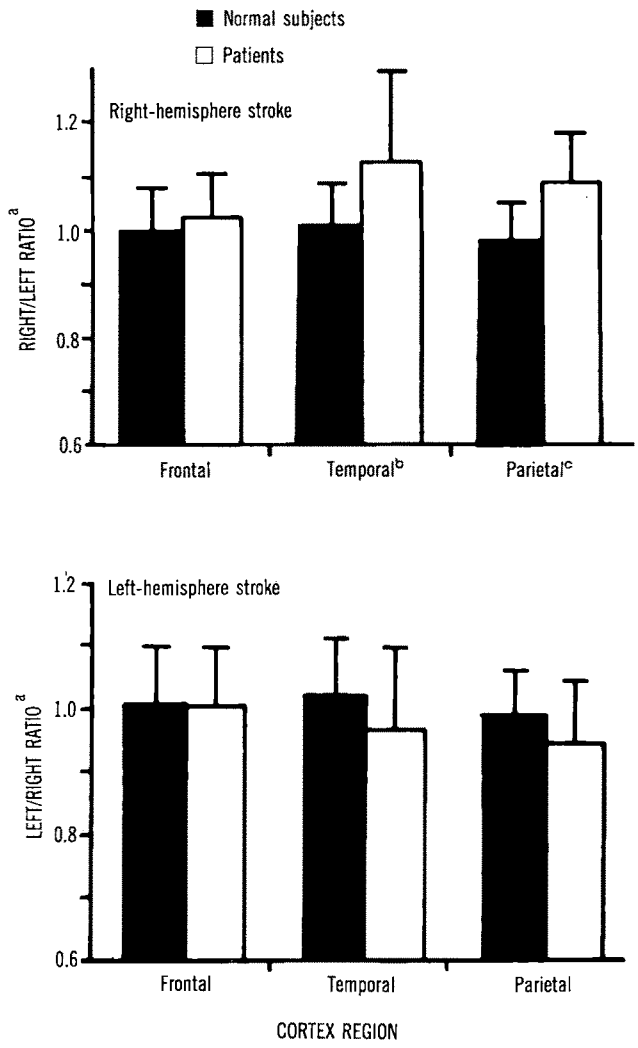
TABLE 3. Neuropsychiatric Test Scores of Patients With Left-Hemisphere or Right-Hemisphere Stroke

	Left-Hemisphere Stroke (N=8)		Right-Hemisphere Stroke (N=9)	
Test	Mean	SD	Mean	SD
Johns Hopkins Functional Inventory	0.50	1.4	3.33	3.7
Mini-Mental State	28.0	1.5	25.4	3.7
Present State Examination	10.1	6.9	14.1	7.3
Hamilton Rating Scale for Depression	9.1	4.0	12.6	5.7
Zung Self-Rating Depression Scale	39.5	11.0	49.6	15.8

0.32 [1 SD]; left-hemisphere strokes=0.768±0.13). Right- versus left-lesion ratios were not significantly different.

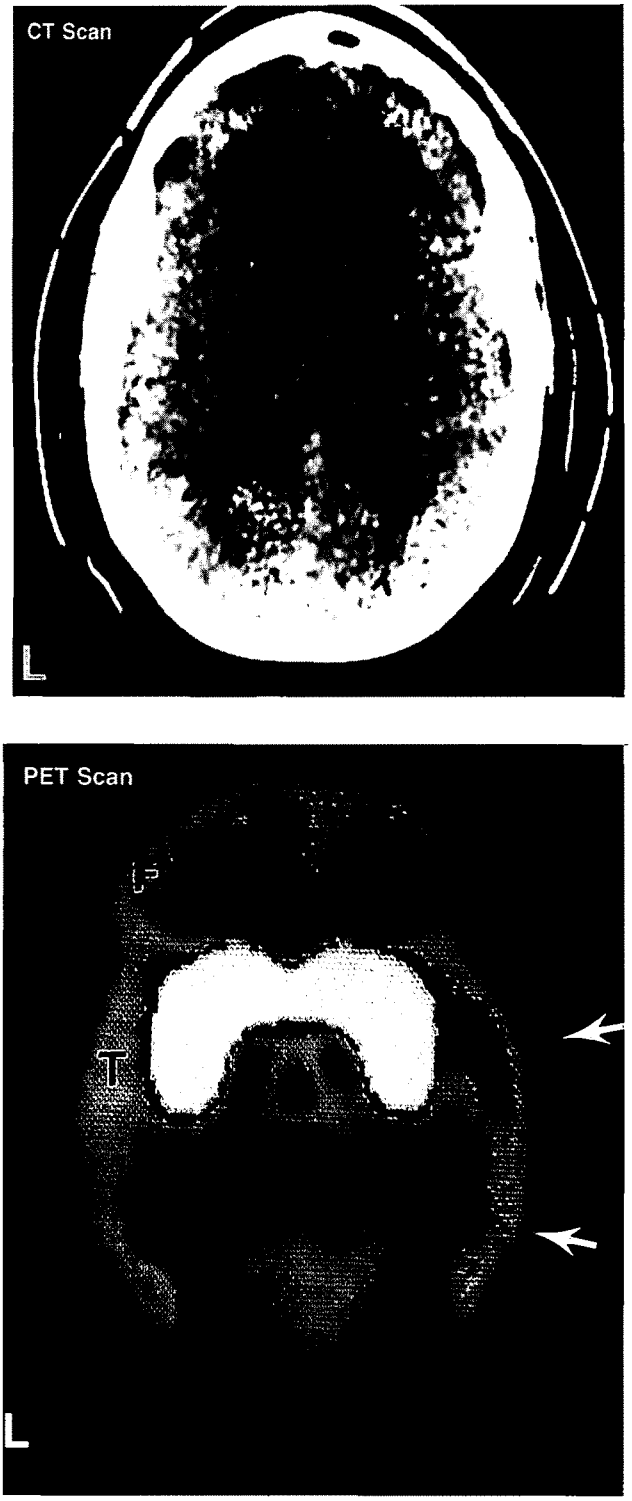
Figure 2 illustrates that there was no right-left asymmetry (i.e., ratio of right to left cortical activity) in NMSP binding in any of the cortical regions measured in normal volunteers. Similarly, patients with left-hemisphere strokes had mean ipsilateral (i.e., left) to contralateral (i.e., right) ratios that were not significantly different from those of non-brain-injured control subjects (two-tailed Student's t tests or Mann-Whitney U test) (lower panel). In contrast, patients with right-hemisphere strokes had significantly higher ipsilateral to contralateral NMSP binding ratios than the control group; these comparisons were made with either nonparametric or parametric statistics in both temporal cortex and parietal cortex but not in frontal cortex (U=93, 60, df=16, p=0.194; t=−0.824, df=16, p=0.42) (upper panel). Figure 3 presents a PET scan (bottom panel) demonstrating this phenomenon, as well as the comparable CT scan, which does not show the lesion. A summed image, 70–90 minutes after NMSP injection, shows increased S_2 receptor binding in the uninvolved temporal (T) but not frontal (F) regions ipsilateral to the stroke lesion (white

FIGURE 2. S_2 Receptor Binding Asymmetry (ratio of counts ipsilateral to contralateral of the stroke) in Patients With Left-Hemisphere (N=8) or Right-Hemisphere (N=9) Stroke and in Normal Subjects (N=17)



[a]A ratio of more than 1 indicates greater S_2 receptor binding on the side of the stroke. Error bars indicate standard deviations.
[b]Mann-Whitney U=116, 37, df=16, p=0.018; t=−2.84, df=16, p=0.009.
[c]U=101, 35, df=16, p=0.029; t=−2.089, df=16, p=0.048.

FIGURE 3. (3-N-[^{11}C]methyl)spiperone (NMSP) Binding in a Patient With a Right Frontal Lobe White Matter Infarct



arrows), compared to mirror regions in the opposite hemisphere.

The mean cortical to cerebellar ratios for contralateral (i.e., uninjured hemisphere) frontal, temporal, and parietal cortex in patients with left-hemisphere strokes were 1.52±0.18 (1 SD), 1.67±0.29, and 1.47±0.29, respectively. These ratios were not significantly different from the ratios for the contralateral cortex of the group with right-hemisphere strokes, which were 1.47±0.365, 1.58±0.49, and 1.39±0.36, respectively. This finding suggests that the relatively higher ipsilateral to contralateral binding ratio in patients with right-hemisphere strokes was due to greater binding in right cerebral cortex rather than less binding in the left.

The cortical to cerebellar ratios both ipsilateral and contralateral to the stroke were lower (although this was not statistically significant) than in normal subjects (e.g., control subjects' temporal cortical to cerebellar ratio=1.88±0.38, frontal=1.66±0.34, parietal=1.55±0.34). This suggests that the greater binding after right-hemisphere stroke is "relative" to binding in the brains of patients with cerebrovascular disease.

Among the patients with left-hemisphere strokes, the ipsilateral to contralateral NMSP binding ratio in the temporal cortex was highly correlated (analysis with either Pearson correlations or Spearman rank correlations) with the Zung depression scale and showed a nearly significant correlation with the Present State Examination and Hamilton depression scale (table 4). In contrast, in the right-hemisphere stroke group, there were no significant correlations between depression scores and NMSP binding ratios. No significant correlations were found between NMSP binding and lesion volume, anterior or posterior location, or ratings of physical or cognitive impairment in either the right- or left-hemisphere group.

DISCUSSION

This study has demonstrated that patients with right-hemisphere strokes, approximately 16 months after injury, had greater cortical NMSP binding in noninjured regions of the ipsilateral temporal and parietal cortex than did patients with similar lesions in the left hemisphere. Secondly, the ratio of ipsilateral to contralateral binding was significantly correlated with severity of depressive symptoms in patients with left-hemisphere strokes.

Several methodological points regarding patient selection and the imaging technique require emphasis. Study participants were predominantly of lower socioeconomic class, in their mid 50s, and were studied late after their presenting illness. The extent to which these findings are time dependent is uncertain. Patients with significant comprehension deficits (patients whose lesions were presumably located in the left parietal-temporal cortex) were excluded because clinical verbal interviews could not be conducted. We were not able to control precisely for such important variables as concurrent and prior medication histories, size or location of stroke, and time from stroke to PET scan. Any or all of these factors may have influenced our results, and the findings from this study should be viewed with

TABLE 4. Spearman Correlations Between PET Ratio[a] and Psychometric Test Scores for Patients With Left-Hemisphere or Right-Hemisphere Stroke

	Left-Hemisphere Stroke (N=8)			Right-Hemisphere Stroke (N=9)		
Test	Temporal	Parietal	Frontal	Temporal	Parietal	Frontal
Present State Examination	−0.762	−0.238	−0.119	0.202	0.276	−0.653
Hamilton Rating Scale for Depression	−0.615	−0.193	0.048	0.226	0.108	−0.795
Zung Self-Rating Depression Scale	−0.929[b]	−0.143	−0.214	−0.383	0.548	−0.633
Mini-Mental State	0.651	−0.012	−0.651	−0.252	0.455	0.042
Johns Hopkins Functional Inventory	−0.412	−0.577	−0.412	0.152	−0.449	−0.582

[a]Ratio of ipsilateral to contralateral activity for each cortical region.
[b]$alpha_i$=0.0033, $p \leq 0.05$, Spearman rank test with Bonferroni correction for multiple comparisons.

these limitations in mind. These findings need to be replicated in other populations of stroke patients. Another important limitation is that the estimation of receptor density and validation of NMSP binding specificity to S_2 in cerebral cortex were not practical due to the unavailability of a pure S_2 antagonist to perform the requisite displacement and blocking studies (13, 23). However, we compared the right and left sides by means of ratios, and the effect of these issues should not have affected lesions in one hemisphere more than the other. In addition, in vitro binding studies in human brain homogenate preparations (24) and in vivo studies in mice (25), both using 3H-NMSP, have demonstrated saturable specific binding in frontal cortex that is displaceable by ketanserin, a potent S_2 receptor blocker, but not by noradrenaline, dopamine, or dopamine antagonists.

Although these findings need to be evaluated with caution, how might they be construed? In previous publications, we have shown a lateralized biochemical response to middle cerebral artery ligation in the rat (26). Following right-hemisphere injury, there was a significant depletion of norepinephrine and dopamine in the locus ceruleus, substantia nigra, and cerebral cortex. Decreases in ipsilateral serotonin concentrations have also been demonstrated after right ventrolateral cortical punch lesions in rats (27) and after vascular lesions in primates (28). In addition, previous studies have shown important physiological and anatomical interactions between the noradrenergic and serotonergic systems (29, 30). Therefore, if a similar biochemical disturbance occurs in humans, depletions of serotonin and norepinephrine, occurring to a greater degree after right-hemisphere than left-hemisphere strokes, might lead to upregulation of S_2 receptors in the right hemisphere.

Previous studies have found that the severity of poststroke depression in chronic patients is significantly correlated with proximity of the lesion to the frontal pole (7, 8). Our finding that the highest depression scores were significantly associated with the lowest NMSP binding ratio in the left temporal region suggests that upregulation of serotonin receptors may play a role in either preventing depression or facilitating recovery. Although the nature of the relationship between receptor changes and depression will require further research, a number of previous studies implicate serotonin alterations as an etiological factor in depression (31–33).

On the basis of the present findings, one might ask why depression correlated significantly with left temporal NMSP binding when there was no difference in depression scores between the right- and left-hemisphere lesion groups. Although we do not know the answer to this question, there are several possibilities. It is likely that the etiologies of all poststroke depressions are not the same. We have recently found that patients who develop depression after right-hemisphere injury have a significantly greater frequency of psychiatric disorder in their families than those with depression after left-hemisphere lesions (S.E. Starkstein, unpublished data). Thus, the mechanisms responsible for depression after left-hemisphere stroke (perhaps related to changes in serotonin receptors) may be different from those responsible for depression after right-hemisphere stroke (perhaps related to genetic vulnerability). Another possible explanation for why NMSP binding only correlated with depression after left-hemisphere stroke is that we were examining patients more than a year after injury. We have previously reported that the relationship between right-hemisphere lesion location and severity of depression changed over the first 6 months following the stroke (34). Early-onset depressions (i.e., those apparent within a few weeks after stroke) may be associated with left frontal lesions and serotonin receptor changes, while delayed-onset depressions may be associated with right-hemisphere strokes and a mechanism not related to serotonin receptors. The issue of why only depression after left-hemisphere stroke was associated with changes in NMSP binding will require further investigation.

To our knowledge, this is the first demonstration of a lateralized biochemical response to ischemic brain injury in humans. It is consistent with a large literature documenting both anatomical and functional asymmetries in human brain (35, 36), and numerous observations of asymmetrical hemispheric contributions to

TABLE 2. Summary Thought Disorder Index Scores of Patients With Right Cortical Damage, Schizophrenia, or Mania

Patient Group	Thought Disorder Score÷Number of Responses[a]		Thought Disorder Score÷Number of Words[b]		Number of Responses[c]		Number of Words[d]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Right hemisphere cortical damage (N=23)	45.68[e]	32.41	0.57[e]	0.33	5.87[f]	1.87	538.00[e]	372.00
Schizophrenia (N=25)	65.36[e]	50.78	0.75[e]	0.58	8.92[e]	4.40	832.00[e]	575.00
Mania (N=20)	51.08[e]	38.36	0.71[e]	0.65	9.95[e]	5.19	716.00[e]	389.00

[a]One-way ANOVA: F=0.63, df=2, 65, n.s.
[b]One-way ANOVA: F=0.79, df=2, 65, n.s.
[c]One-way ANOVA: F=7.18, df=2, 65, p<0.01.
[d]One-way ANOVA: F=2.17, df=2, 65, n.s.
[e]Significantly different from scores in same column with superscript f (p<0.01, Student-Newman-Keuls).
[f]Significantly different from scores in same column with superscript e (p<0.01, Student-Newman-Keuls).

ular manner of responding that also features extreme fabulizing and associative elaboration.

The second factor that differentiated the patient groups was fragmented thinking. Patients with right hemisphere cortical damage exhibited significantly more of this kind of thinking disorder than did the other patients.

Schizophrenic patients scored significantly higher than the other patients on the third factor, idiosyncratic verbalization. The incoherence category, which is included in this factor, represents the most severe form of disorganization scored by the Thought Disorder Index, and the first four variables constituting this factor represent forms of idiosyncratic slippage at each of the four levels of severity.

No statistically significant differences were discernible for associative looseness and arbitrary thinking, the two remaining factors, although weak trends indicated that manic patients showed more of the former and schizophrenic patients more of the latter.

Total Thought Disorder Index Score

The three groups were not significantly different on either of the two summary total Thought Disorder Index scores, the first using a correction for number of responses and the second using a correction for number of words (see table 2). For comparison, note that normal control subjects tested by Johnston and Holzman (8) received much lower total Thought Disorder Index scores than any of the groups tested here (the normal subjects' mean±SD score for thought disorder ÷responses×100=4.46±3.72). The patients with right hemisphere damage gave significantly fewer responses than either manic or schizophrenic patients, and they also displayed significantly less thought disorder when the Thought Disorder Index was not corrected for verbal productivity.

The relative constriction of response productivity and of thought disorder when uncorrected for verbal productivity shown by patients with right hemisphere damage may reflect an age effect, since these patients were significantly older than those in the other two groups. To address this possible confounding factor of age and responses or uncorrected total Thought Disorder Index score, the group of patients with right hemisphere damage was split into two subgroups at the median age of 72 so that verbal productivity and total Thought Disorder Index scores produced by the two subgroups could be compared. The older subgroup comprised 12 patients aged 72 to 85 with a mean age of 78.1 years; the younger subgroup comprised 11 patients aged 35 to 70 with a mean age of 56.2 years. This comparison showed that the two subgroups did not differ significantly with respect to the number of responses produced (t=1.0, df=21, n.s.) or the total amount of thought disorder evidenced (t=1.49, df=21, n.s.), suggesting that it was not age but right hemisphere damage itself which resulted in constricted production of responses and total amount of uncorrected thought disorder.

Levels of Severity

Manic and schizophrenic patients showed significantly more thinking disorders at the 0.75 level than did patients with right hemisphere cortical damage (F=16.7, df=2, 65, p<0.0001), and schizophrenic patients displayed significantly more of the most severe, 1.0-level disorders than the other two groups (F=10.6, df=2, 65, p<0.0001). In contrast, the least severe slippages (0.25 level) were common in all three groups and no significant differences were noted (F=0.44, df=2, 65, n.s.). Every patient exhibited at least one such cognitive slip, and at least 90% of the patients in each group exhibited three or more instances of thought disorder at the 0.25 level. The groups also did not differ significantly in production of 0.50-level responses (F=0.07, df=2, 65, n.s.).

DISCUSSION

Although serious thinking disorders were exhibited by patients in all three groups, each group produced a unique thought disorder profile.

Patients with right hemisphere damage exhibited significantly more fragmented thinking than did manic or schizophrenic patients. This tendency was manifested on the Rorschach Test as an inability to integrate disparate elements into a total schema. When patients with right hemisphere damage gave more than one response to a Rorschach card, their responses tended to be fragments of a whole percept rather than separate percepts. For example, one patient produced these three responses to one card: "A masquerade party costume," "Cha-cha," and "Clap hands, let's dance." During the inquiry the patient was asked whether "clap hands, let's dance" was something different from "cha-cha," and she responded affirmatively. Later she was asked if she saw a couple doing a dance, and she responded affirmatively again. Then the examiner said, "And how about cha-cha, was that a similar thing?" and the patient replied, "Um hm." Thus the patient was able to integrate her responses only when the examiner asked her if she saw a couple doing a dance, whereas earlier she had said that her responses were different from each other. Her inability to integrate the perceptual material into a whole percept resulted in a fragmented response.

The inability to integrate elements to form a coherent whole was also reflected in these patients' tendency to focus on one small part of the inkblot while ignoring the remainder. For instance, one patient, pointing to a small part of the blot, said, "That looks like a handle." When saying this, the patient made a grabbing motion and then said, "Looked like you could take it, you know."

Moreover, when these patients did attempt to respond to the whole blot, their utterances were frequently vague or confused, as in the following two examples: "Well, it's something . . . with two . . . equal . . . parts. Or two equal sides." "Heads were mostly . . . hairs so uneven . . . he-hairs not—, bodies were so uneve-, uneven. Well, they weren't . . . close together . . . some were . . . longer than others."

In an earlier study that used the Rorschach Test to characterize ideational processes associated with unilateral brain damage, Hall et al. (3) found that patients with right hemisphere lesions showed an expansive, uncritical pattern of thinking. These patients used many determinants freely to create bizarre interpretations of the blots. There was a noteworthy absence of congruity between the percept and the blot.

A similar inability to integrate elements properly and to evaluate constructs is demonstrated in the absurd, uncritical interpretation of metaphors by patients with right hemisphere damage (21), their analyses of humorous material (2, 22), and their failure to integrate verbal elements to make a coherent narrative (7, 23).

Constructional apraxia, the deficit most commonly recognized as associated with right hemisphere damage (24), has also been described as an inability to integrate disparate elements to create a coherent schema. Yet, although this deficit has often been viewed as reflecting impairment in specific visuospatial processes, it may be another consequence of the more general inability to evaluate the interrelationship among elements in the context of an overall pattern, as seen in verbal tasks here and in other studies. In conformity with this formulation, the degree of visuospatial impairment measured after right hemisphere damage correlates highly with deficits in recalling and interrelating elements from verbal narrative material (25). This finding suggests that both the visuospatial and the verbal deficits of these patients may stem from a common underlying loss in integration of thoughts (26).

Manic thought disorder assumed a different character from that displayed by patients with right hemisphere damage. Manic patients showed significantly more combinatory thinking than patients in the other two groups. They often responded in an overly flippant manner, and their playfulness tended to carry them beyond reality constraints into extreme associative elaboration. Schizophrenic thought disorder, in contrast, often consisted of a mismatch between ideas and words. Schizophrenic patients produced significantly more idiosyncratic verbalizations than the other two groups, reflecting arbitrary and odd word choices that often rendered their responses incomprehensible to others. The nature of thought disorder exhibited by manic and schizophrenic patients has been described in detail elsewhere (10, 11).

In summary, in this first explicit comparison of the thinking disorders of manic patients, schizophrenic patients, and patients with right hemisphere cortical damage, we found different profiles of thought disorder among these diagnostic groups. These unique patterns may constitute useful criteria for diagnoses, and they provide additional support for the view that thought disorders differ among neuropsychiatric conditions. In addition, it is clear from this study that right hemisphere damage produces a pervasive but not extremely severe disorder of integration of thoughts. This thinking disorder may escape detection in clinical settings, quite possibly because of the intact surface structure of language in patients with right hemisphere lesions.

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Somatization and Depression in Fibromyalgia Syndrome

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Psychiatric diagnoses, self-reports of symptoms, and illness behavior of 20 fibromyalgia patients and 23 rheumatoid arthritis patients were compared. The fibromyalgia patients were not significantly more likely than the arthritis patients to report depressive symptoms or to receive a lifetime psychiatric diagnosis of major depression. These results do not support the contention that fibromyalgia is a form of somatized depression. Fibromyalgia patients, however, reported significantly more somatic symptoms of obscure origin and exhibited a pattern of reporting more somatic symptoms, multiple surgical procedures, and help seeking that may reflect a process of somatization rather than a discrete psychiatric disorder.

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Fibrositis syndrome, or fibromyalgia, is a common rheumatic condition characterized by chronic and usually diffuse musculoskeletal pain (1). Symptoms involve primarily soft tissue, with acute tenderness on pressure—"tender points"—at many specific anatomical sites, including bony prominences, muscle insertions, and the bodies of certain muscle groups. Fibromyalgia also frequently includes nonrestorative sleep (failing to awaken refreshed), fatigue, malaise, headache, and symptoms of irritable bowel syndrome (2). Since there is no generally accepted organic pathology in fibromyalgia, it constitutes a clinically important example of a functional somatic syndrome (3).

Although a psychogenic cause of fibromyalgia has been repeatedly proposed, results of studies that use measures of psychological distress have been equivocal, and only modestly elevated scores on the MMPI hysteria and hypochondriasis scales have been noted (4–7). Hudson et al. (8) administered the National Institute of Mental Health Diagnostic Interview Schedule (DIS) to 31 patients who met the criteria of Yunus et al. (2) for fibromyalgia. Seventy-one percent of the patients had a history of major depression, and 26% were currently suffering from an episode of major depression. Separate family history interviews revealed a significantly greater prevalence of major depression among the relatives of fibromyalgia patients than among comparison groups of relatives of patients with rheumatoid arthritis or schizophrenia. However, most of the reported depressive episodes in the fibromyalgia patients occurred long before the onset of fibromyalgia syndrome (9), and only one of 23 patients given the dexamethasone suppression test displayed nonsuppression of cortisol (10).

While fibromyalgia may be a variant form of major depressive disorder with prominent somatic symptoms, the polysymptomatic picture is also reminiscent of *DSM-III* somatization disorder (11). Although Hudson et al. (8) found only a 6% rate of somatization disorder among their sample of fibromyalgia patients, they did not report on other indications of somatization that might not be included in the *DSM-III* criteria.

The present study was designed to examine more closely the presence and coexistence of depression and somatization in fibromyalgia patients. Standardized diagnostic procedures as well as measures of affective and somatic symptom reporting were applied to a group of patients with fibromyalgia and a comparison group of patients with rheumatoid arthritis.

METHOD

Subjects were drawn from the practice of one Montreal-based rheumatologist (M.A.K.). Patients currently receiving compensation or involved in litigation related to their disabilities were excluded. Twenty consecutive patients who met the criteria of Yunus et al. (2) for fibromyalgia were enrolled in the study. We used 16 tender points as diagnostic criteria, and patients in this group reported sensitivity at an average of 8.8 points. All of these patients also reported diffuse musculoskeletal pain or stiffness and nonrestorative sleep.

Twenty-three patients drawn from the same physician's practice who met the American Rheumatism Association criteria for classic or definite rheumatoid arthritis (12) served as a comparison group. Patients

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with rheumatoid arthritis were selected for comparison because they suffer from chronic debilitating joint disease with symptoms that often resemble those of fibromyalgia.

Of the 20 fibromyalgia patients enrolled in the study, all but one were women; there were six men among the 23 rheumatoid arthritis patients. The mean±SD age and education levels were very similar for the two groups. The age of the fibromyalgia patients was 58.7±13.0 years, and the age of the rheumatoid arthritis patients was 57±11.2 years. Fibromyalgia patients had had 11.5±3.0 years of schooling, and the rheumatoid arthritis patients had had 11.7±2.9 years. Seventy percent (N=14) of the fibromyalgia group and 57% (N=13) of the rheumatoid arthritis group were working full or part time. Slightly fewer fibromyalgia patients (50%, N=10) than rheumatoid arthritis patients (65%, N=15) were married.

All subjects were interviewed using version 3 of the DIS (13), a structured psychiatric diagnostic instrument that can be administered by trained lay interviewers. Only those portions of the DIS which are necessary for making diagnoses of major depression and somatization disorder with exclusion criteria were used, in order to shorten interview time.

The DIS is known to underdiagnose somatization disorder because lay interviewers are often unable to distinguish between a valid medical explanation for somatic symptoms and an invalid one (14). Each subject's responses were reviewed by a clinical psychiatrist (L.J.K.) to ensure that medical explanations offered by patients for somatic symptoms could, in fact, account for those symptoms (14, 15). Fibromyalgia and rheumatoid arthritis were accepted as valid medical explanations for symptoms commonly recognized as part of the clinical syndromes.

All subjects completed the Center for Epidemiologic Studies Depression Scale (CES-D) (16) and a modified version of the SCL-90 somatization scale (17). The CES-D consists of 20 items characteristic of clinical depression and has been shown to be a reliable screening instrument for major depression in community surveys (18).

The SCL-90 somatization scale consists of 12 items pertaining to common somatic symptoms. We modified the scale to a response format consistent with that of the CES-D, in which a subject's score represents the sum of the number of somatic symptoms experienced during the preceding week weighted by the frequency of duration of each symptom. Among family medicine patients the modified scale has been shown to correlate at 0.30 or above with body awareness, worry that one has a serious illness, and a bias toward attributing vague symptoms to somatic illness rather than emotional distress (19).

Twelve months after the initial interview evaluation and medical chart review, subjects were recontacted by a research assistant to inquire about their feelings of nervousness and depressed mood and their use of health care services over the past year.

TABLE 1. Lifetime Psychiatric Diagnoses of Patients With Fibromyalgia Syndrome and Rheumatoid Arthritis

Diagnosis	Fibromyalgia Patients (N=20)		Rheumatoid Arthritis Patients (N=23)		General Population (%)[a]
	N	%	N	%	
Major depression	4	20.0	2	8.7	5.2
Dysthymic disorder	0	0.0	3	13.0	3.0
Obsessive-compulsive disorder	1	5.0	1	4.4	2.5
Agoraphobia	1	5.0	1	4.4	6.1
Somatization disorder	1	5.0	0	0.0	0.4

[a]Percentages are from reference 20, except for the percentage for somatization disorder, which is from reference 15.

RESULTS

The lifetime psychiatric diagnoses ascertained by the DIS are presented in table 1. Although 20 percent (95% confidence interval=0.375 to 0.025) of the fibromyalgia patients fulfilled criteria for a major depressive episode at some time in their lives, compared with 8.7% (95% confidence interval=0.202 to −0.028) of the rheumatoid arthritis patients, there were no significant differences, by chi-square test, between the two groups. Statistical power analysis indicates that the likelihood of our having missed a true prevalence of depression among the fibromyalgia patients of 71%, as reported by Hudson et al. (8), is less than 0.001 (21).

There was no significant difference in number of depressive symptoms, as measured by the CES-D, between fibromyalgia patients (mean±SD=15.05±9.7, 95% confidence interval=34.10 to −3.92) and rheumatoid arthritis patients (11.9±11.9, 95% confidence interval=35.22 to −11.42) (t=0.94, df=41, p=0.35, two-tailed). At 12-month follow-up, 45% (N=9) of the fibromyalgia subjects and 9% (N=2) of the rheumatoid arthritis subjects reported a lot of trouble with nerves or nervousness (χ^2=5.78, df=1, p=0.02). At 12-month follow-up, there was a trend for more fibromyalgia patients than rheumatoid arthritis patients to report a 2-week period of depressed mood during the preceding year (50%, N=10, and 22%, N=5, respectively) (χ^2=2.25, df=1, p=0.10). There was no significant difference between groups in the number of times each had talked with a physician about nerves or emotional worries in the preceding 12 months (for the fibromyalgia patients, mean±SD=2.42±6.84; for the rheumatoid arthritis patients, 0.45±1.4) (t=1.32, df=39, p=0.20, two-tailed). The large variance in the fibromyalgia group was due mostly to one patient who had received multiple sessions of psychological counseling.

The *DSM-III* diagnosis of depression depends on patients' ability to recall a period of 2 weeks or more of dysphoric mood. Some patients may suffer from "masked" depressions, in which they downplay or do

Table 2. Lifetime Vegetative Symptoms of *DSM-III* Major Depression in 20 Patients With Fibromyalgia Syndrome and 23 Patients With Rheumatoid Arthritis

Vegetative Symptoms of *DSM-III* Major Depression	Symptoms				
		Fibromyalgia Patients		Rheumatoid Arthritis Patients	
	N[a]	Mean	SD	Mean	SD
All vegetative symptoms	9	1.45	1.6	0.87	1.3
Poor appetite or weight loss or gain	3	0.40	0.7	0.30	0.6
Insomnia or hypersomnia	2	0.45	0.6	0.26	0.5
Psychomotor agitation or retardation	2	0.05	0.2	0.13	0.3
Anhedonia	1	0.15	0.4	0.04	0.2
Fatigue	1	0.40	0.5	0.13	0.3

[a]Number of items in symptom category.

not report the affective component of the depressive syndrome. In order to look for possible masked depression, we examined the lifetime prevalence of vegetative symptoms of depression among all the subjects, whether or not they reported a prolonged period of dysphoric mood. As table 2 shows, fibromyalgia patients differed very little from rheumatoid arthritis patients on vegetative symptoms of depression, with the single possible exception of fatigue. To protect against the risk of type I errors when multiple t tests are performed, a multivariate comparison was computed (22). When the fibromyalgia vector of five means corresponding to the five vegetative symptoms of depression was compared to the rheumatoid arthritis vector of those means, the difference was not significant (Hotelling's $T^2=29.7$; $F=1.41$, $df=5, 37$, $p=0.24$). Thus, separate t tests were not computed.

The fibromyalgia patients reported significantly more symptoms on our modification of the somatization scale of the SCL-90 (fibromyalgia patients' mean±SD=12.0±5.8; rheumatoid arthritis patients', 7.56±5.8) ($t=2.50$, $df=41$, $p=0.02$, two-tailed). While only one patient with fibromyalgia fulfilled the *DSM-III* criteria for somatization disorder, fibromyalgia patients reported significantly more somatic symptoms with no medical explanation than did rheumatoid arthritis patients (see table 3). Table 3 also presents the somatic symptoms that contribute to the diagnosis of somatization disorder grouped according to functional system. Multivariate comparison of the fibromyalgia vector of eight means corresponding to functional systems and the rheumatoid arthritis vector of these eight means indicated that fibromyalgia and rheumatoid arthritis patients differed in the number of somatic symptoms that had received no medical explanation (Hotelling's $T^2=28.4$; $F=2.94$, $df=8, 34$, $p=0.01$). Consequently, univariate t tests were computed. In these tests, fibromyalgia patients reported more medically unexplained symptoms in all functional systems; the difference reached significance for conversion symptoms, headache, other pain, and cardiopulmonary symptoms. One-third (N=7) of the fibromyalgia patients, but no rheumatoid arthritis patients, reported that they had been sickly most of their lives. Five fibromyalgia patients, but no rheumatoid arthritis patients, had stayed home from work for 2 weeks or longer without a medical explanation.

The fibromyalgia and rheumatoid arthritis patients also differed in their illness behavior. Fibromyalgia patients saw a mean±SD of 3.1±3.4 different physicians before visiting the rheumatologist, compared to only 1.3±0.9 for the rheumatoid arthritis group ($t=2.42$, $df=41$, $p=0.02$, two-tailed). Although the two groups had had comparable numbers of surgical procedures, when operations on joints were eliminated, fibromyalgia patients had had a mean±SD of 3.1±2.4 other operations; the rheumatoid arthritis patients had had 1.77±1.4 ($t=2.19$, $df=40$, $p=0.03$, two-tailed).

DISCUSSION

In contrast to the study by Hudson et al. (8), our findings do not support major depression as a common correlate of fibromyalgia syndrome. Only one in five of our fibromyalgia patients had ever had an episode of major depression, and in most cases this was long before the onset of fibromyalgia syndrome. Despite our small sample size, the chance of our having missed in our study a true prevalence of major depression of the magnitude that Hudson et al. found in their study is less than 0.001. The discrepancy between our results and those of Hudson et al. may reflect differences in administration of the DIS. In the Hudson et al. study, an experienced research psychiatrist administered the DIS, allowing for more skillful detection of equivocal symptoms, particularly among patients reluctant to acknowledge emotional distress. However, any such limitation in our study should have shown itself as a lower prevalence of depression in the rheumatoid arthritis patients than in Hudson et al.'s patients. This did not happen.

A more likely explanation for the discrepancy between the results of the two studies is variation in the clinical populations and sampling. Recently, Goldenberg (9) extended the original Hudson et al. series by an additional 51 patients. Of a total sample of 82 fibromyalgia patients, 46% had a history of major depression, and only 13% were found to have a current depressive episode. This extended series suggests that Hudson et al.'s original report was inflated by sampling error. In addition, fibromyalgia patients in our sample differed in important ways from those reported by Hudson et al. (8) and others (2). Our fibromyalgia patients were somewhat older, on average, than those in Hudson et al.'s study (58.7 years and 45.1 years, respectively), had been ill for a shorter time (3.4 years and 5.3 years), and reported somewhat fewer tender points (8.8 and 13.5). These sampling differences may reflect differences in Canadian and U.S. health care

TABLE 3. Lifetime Somatic Symptoms of 20 Patients With Fibromyalgia and 23 Patients With Rheumatoid Arthritis

Somatic Symptoms Without Medical Explanation[a]	Symptoms						
		Fibromyalgia Patients		Rheumatoid Arthritis Patients		t	p
	N[b]	Mean	SD	Mean	SD	(df=41)	(two-tailed)
Total	40	5.65	3.7	1.91	1.7	4.39	<0.001
Sickly most of life	1	0.30	0.5	0.00	0.0	3.07	0.004
Conversion or pseudoneurological	15	0.95	1.2	0.17	1.4	2.78	0.008
Gastrointestinal	6	1.00	1.2	0.48	0.7	1.83	0.075
Female reproductive	4	0.65	0.9	0.39	0.7	1.02	0.312
Psychosexual	3	0.70	0.7	0.35	0.6	1.88	0.067
Pain	6	0.75	1.0	0.13	0.5	2.74	0.009
Headache	1	0.35	0.5	0.09	0.3	2.18	0.035
Cardiopulmonary	4	0.95	0.9	0.30	0.6	2.89	0.006

[a]All symptoms of *DSM-III* somatization disorder included in the Diagnostic Interview Schedule plus headache.
[b]Number of items in symptom category.

systems. The fee-for-service structure of the U.S. health care system may select for greater pathology than the Canadian system of universal health insurance (23). Accordingly, patients in Montreal who have fibromyalgia symptoms but not concurrent depression may seek medical help more readily than their American counterparts.

Compared with the rheumatoid arthritis patients, the fibromyalgia patients in this study did not report higher levels of depressive symptoms or vegetative symptoms in the absence of the full depressive syndrome. These results, which are consistent with those of other recent studies of depressive symptoms in fibromyalgia and rheumatoid arthritis patients that have used the MMPI depression scale or the Zung Self-Rating Depression Scale (4, 5, 7, 24), do not support the view of fibromyalgia as a form of masked or somatized depression.

Most fibromyalgia patients also do not meet the *DSM-III* criteria for somatization disorder. However, as a group, fibromyalgia patients do report more frequent and more varied somatic symptoms in many functional systems, including somatic symptoms without medical explanation. Fibromyalgia patients show other features characteristic of somatization disorder. They are more likely to visit multiple physicians and have more frequent surgical procedures for problems that are not musculoskeletal. To some extent this may reflect physicians' difficulty in reaching a diagnosis for these patients' varied symptoms. Fibromyalgia patients are more likely to view themselves as sickly and to miss time from work for medically unexplained illness.

The concept of somatization disorder as a discrete clinical entity is inadequate for characterizing the fibromyalgia patients in this study, who displayed high levels of symptom reporting and help-seeking behavior without fulfilling the criteria for the *DSM-III* diagnosis. An approach to somatization as a process of illness behavior may be more useful (25). In this view, somatization could result from social-psychological processes, including increased focus on the body, hypochondriacal worry, and attributing emotional distress to somatic causes, which lead to more symptom reporting and help seeking (19). The study of illness behavior may provide new diagnostic and therapeutic approaches to patients with somatic symptoms of obscure origin (26).

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A New Scale for the Assessment of Depressed Mood in Demented Patients

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Twenty-one subjects with clinically diagnosed dementia of the Alzheimer type were rated on the Dementia Mood Assessment Scale, a new instrument intended to measure the severity of depressed mood in cognitively impaired patients. Ratings were based on direct observation and a semistructured interview of the patient. Interrater reliability was established. There were highly significant correlations between patients' scores on the instrument's 17-item depression subscale and their scores on global measures of depression and sadness. The potential usefulness of this new scale in assessing the severity of depression in demented patients longitudinally or under drug treatment conditions is discussed.

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Depression frequently accompanies dementia. In fact, estimates of concurrent depressive symptoms in patients with dementia have ranged as high as 30%–50% (1–5). Most previous reports of coexistent depression and dementia have relied on clinical observation, general diagnostic criteria, or rating instruments originally designed for nondemented depressed subjects (6–10). However, because cognitive impairment is the characteristic clinical manifestation of dementia, the traditional psychiatric tools for the assessment of mood may be of limited value. Thus, there is need for a rating instrument to measure the severity of depression, particularly over time, in this population.

Since the "gold standard" of rating instruments in depression research has for many years been the Hamilton Rating Scale for Depression (11–13), why not simply apply that scale to dementia patients and avoid introducing yet another rating scale? First, the Hamilton scale was originally designed for patients already diagnosed as suffering from depressive disorder and has never been validated for dementia patients. Second, while the Hamilton scale is clinically helpful, our experience indicates that it does not fully address mood-related features in cognitively impaired patients and may give inappropriate weight to the frequent somatic complaints generally seen in the elderly. Third, and perhaps most important, several of the questions on the Hamilton scale may require cognitive capacities beyond the level of some demented patients (i.e., items concerning feelings of guilt, work and activities, and insight) and thus may not accurately reflect underlying mood.

Because of the potential therapeutic implications of determining the severity of concurrent depression (4) and the paucity of adequate rating tools to measure the degree of depression in dementia patients (6), we developed the Dementia Mood Assessment Scale, a brief instrument for the measurement of mood in such patients. The scale was designed for use by trained raters on the basis of clinical observation and a semistructured interview and grew out of our previous experience with the Hamilton scale for these patients. The Dementia Mood Assessment Scale is intended to be used as a measure of the degree or intensity of depressive mood in cognitively impaired subjects, not as an instrument for the diagnosis of depression. In this report, we present our preliminary experience with the scale and our attempts to establish its reliability and validity for patients with dementia of the Alzheimer type.

METHOD

Twenty-one patients with dementia of the Alzheimer type were tested with the Dementia Mood Assessment Scale. The subjects were hospitalized at the National Institute of Mental Health, where they were undergoing cognitive and biochemical tests in preparation for drug protocols. All of the patients had been drug free

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for at least 14 days at the time of the rating. The diagnosis of primary degenerative dementia or probable Alzheimer's disease had been established according to *DSM-III* criteria or the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke (14), respectively. Patients with diabetes mellitus, severe hypertension, history of strokes, alcoholism, Parkinson's disease, or other major medical illnesses were excluded from the study. None of the subjects met the *DSM-III* criteria for a major affective disorder at the time of the study, although two individuals had histories of depression. The severity of dementia was judged at the time of admission by physicians using the Clinical Dementia Rating Scale (15) and the Global Deterioration Scale (16). The Hamilton depression scale (11) was also administered at the time of admission. Patients were excluded from the study if they were unable to provide informed consent for this procedure. The group consisted of 13 women and eight men whose mean±SD age was 66.9±10.2 years (range=42–74 years).

The Dementia Mood Assessment Scale is a 24-item scale designed to focus on the observable mood and functional capacities of dementia patients. While the scale is in part derived from the Hamilton depression scale, special efforts were taken to formulate the questions so that they could be addressed objectively. Most of the items are scaled from 0 (within normal limits) to 6 (most severe), with intermediate descriptors intended to serve as general indicators of increasing severity. The first 17 items were determined a priori to be the most representative of mood in dementia patients on the basis of our clinical experience. The remaining seven items were included as related and perhaps important variables in the assessment of overall severity of dementia, but they were not intended to measure mood per se. The Dementia Mood Assessment Scale score was considered to be the sum total for the first 17 items. (The 24-item scale is available from the authors on request.)

Each of the 21 patients was interviewed for approximately 20-30 minutes by a rater trained in the use of the dementia mood scale. The remainder of the consensus raters observed the interview through a one-way mirror to minimize the anxiety caused by the rating procedure itself. The pool of raters, all members of the clinical research team, included five physicians, a social worker, eight nurses, and two clinical research assistants. The initial training of all raters included general orientation about the purpose of the rating instrument and several practice sessions. (An expanded set of guidelines for all questions on the Dementia Mood Assessment Scale was also developed for training purposes and is available on request from the authors.) Six of the raters (T.S., I.S.A., D.Y., P.N.T., P.A.N., and E.A.M.) were considered "core" raters (for the purpose of statistical analysis only) because it was assumed that their greater experience with the development of the scale might lead to higher interrater reliability. The other raters consisted primarily of nursing unit staff members who had daily contact with the patients before and after the interview. Once the interview was completed, the raters independently scored the scale, taking into account what they had observed during the interview as well as the unit staff's general observations of the events of the preceding week. Documented observations of the nursing staff (i.e., sleep record, weight, eating habits, and general activity reports) were available to all raters before the consensus ratings were made. Each subject was rated by four to 12 observers (average=7.2 raters per subject); there was a total of 151 ratings for the 21 subjects.

As a possible standard reference, the patients were also rated on each of eight global measures according to a modification (17) of guidelines originally intended for rating depressed patients (18). The areas covered included depression, sadness, functional impairment, cognitive impairment, psychosis, mania, anxiety, and anger. The global measures of impairment, anger, and sadness were new measures introduced in this study, each with separate guidelines (available from the authors on request). The global scores can range from 0 to 15. These global measures were scored for each patient after the interview had been completed and were also based on the preceding week's behavior.

Interrater reliability for the total Dementia Mood Assessment Scale 17-item score was assessed by using the intraclass correlation coefficient (ICC) from a two-way analysis of variance (19). This measure of "reliability," or numerical correspondence of scores, was used because it is interpretable as the proportion of the variance among a series of measurements of a group of subjects that is due to between-subject variability (20). Pearson correlation coefficients were used in examining the linear relationships between dementia mood scale scores, global scores, and various baseline measures. Spearman rank correlation coefficients were also calculated, but because they provided no substantive changes in the data analysis, only the Pearson correlations are presented. All test statistics reported are significant at the 0.001 level or better unless otherwise noted. Statistical Analysis System procedures (SAS Institute, Cary, N.C.) were used for the correlations.

RESULTS

The subjects' ratings on the Dementia Mood Assessment Scale were generally in the mild to moderate range. The mean±SD duration of symptoms was 4.3±3.4 years (range=1.5–15.0 years). (Duration was defined on admission as the number of years since the onset of dementia symptoms severe enough to warrant consulting a physician.) On the Clinical Dementia Rating Scale, the subjects' mean±SD score was 1.6±0.6; range=1–3 (0=normal, ½=questionable dementia, 1=mild, 2=moderate, 3=severe). On the Global Deterioration Scale, the score was 4.1±0.9; range=3–6 (1=normal, 7=very severe dementia). The correlation (r=0.81) between the scores on these two severity

TABLE 1. Scores of 21 Dementia Patients on the 17-Item Subscale of the Dementia Mood Assessment Scale and on Global Measures

Measure	Score		
	Mean	SD	Range
Dementia Mood Assessment Scale (17-item subscale)[a]	25.2	9.3	4–41
Global measures[b]			
Depression	4.9	2.2	1–13
Sadness	5.9	2.2	1–13
Functional impairment	8.0	2.0	4–12
Cognitive impairment	8.0	1.9	4–12
Psychosis	2.0	1.1	1–6
Mania	1.4	1.8	1–6
Anxiety	4.9	1.5	2–8
Anger	4.3	2.2	1–10

[a]Most items were scored from 0 (within normal limits) to 6 (most severe).
[b]Global measures were rated from 0 to 15 (0–3=within normal range, 4–6=mild, 7–9=moderate, 10–12=severe, 13–15=very severe).

TABLE 2. Intraclass Correlation Coefficients for Ratings of 21 Dementia Patients on the 17-Item Subscale of the Dementia Mood Assessment Scale and on Global Measures by Core and Other Raters

Measure	Intraclass Correlation Coefficient	
	Core Raters[a]	Other Raters[a]
Dementia Mood Assessment Scale (17-item subscale)	0.74[b]	0.69[b]
Global measures		
Depression	0.67[b]	0.72[b]
Sadness	0.62[b]	0.60[b]
Functional impairment	0.77[b]	0.64[b]
Cognitive impairment	0.72[b]	0.65[b]
Psychosis	0.78[b]	0.63[b]
Mania	0.64[b]	0.28[c]
Anxiety	0.47[b]	0.41[d]
Anger	0.64[b]	0.57[b]

[a]There were 68 ratings by core raters and 83 by other raters in 21 consensus meetings, for an average of 3.2 core and 4.1 other raters at each meeting.
[b]$p<0.0001$.
[c]$p<0.01$.
[d]$p<0.001$.

scales was highly significant, suggesting a high degree of consistency across these two baseline measures. On the Hamilton depression scale, which was given on admission, 1–6 weeks before the consensus conference, the patients' mean score was 8.8±3.8 (range=0–14).

The mean 17-item dementia mood scale score and the scores on the eight individual global scales are listed in table 1. They reveal a group of patients who were mildly to moderately affected in terms of both dementia and depression. As can be seen in table 2, the core and the other raters showed considerable interrater reliability in using the Dementia Mood Assessment Scale, with highly significant ICCs. In fact, the only obvious difference between the two groups of raters occurred on the global ratings for mania.

To address the central issue of how well the Dementia Mood Assessment Scale reflects the clinical impression of depression, the 17-item total score was correlated with the global scores. The association was highly significant for both depression ($r=0.73$) and sadness ($r=0.65$) (table 3). By contrast, the correlations between the Hamilton depression score and the scores on global measures of depression and sadness were somewhat less significant ($r=0.39$ and $r=0.43$, respectively). The overall correlation between the 17-item dementia mood scale score and the Hamilton depression score was 0.47. There were weaker correlations between the 17-item score and the global measures of anxiety and anger ($r=0.30$, $p=0.012$, and $r=0.34$, $p=0.004$, respectively). It is notable that the total score on items 18–24 of the Dementia Mood Assessment Scale (the sum of the last seven items), which was intended to help classify the severity of a patient's dementia, was significantly correlated with the scores on the global measures of functional and cognitive impairment ($r=0.49$ and $r=0.46$, respectively) (table 3). The psychosis global score was also correlated with the total score on items 18–24 ($r=0.31$, $p=0.01$). As can be seen in table 3, eight of the first 17 individual dementia mood scale items had highly significant correlations with the global measure of sadness, and seven of the 17 were correlated with the global score for depression. No other global measure was significantly correlated with more than two of the first 17 dementia mood scale items.

There was no significant correlation between either duration of dementia symptoms or severity of dementia and any of the mood ratings used in this study. As expected, there were significant correlations between scores on the overall dementia scales (Clinical Dementia Rating Scale and the Global Deterioration Scale) and the global scores on cognitive and functional impairment ($r=0.49$ and $r=0.71$, respectively).

DISCUSSION

Establishing the validity of a new scale for the measurement of depressed mood in dementia in the absence of a previously accepted uniform standard is difficult at best. While the highly significant correlations between the Dementia Mood Assessment Scale score and the global scores for both depression and sadness do not certify the validity of measuring the mood of dementia patients with this scale, they do suggest a strong relationship. The significant correlation between scores on the dementia mood scale and the Hamilton depression scale is not surprising given the general overlap of questions on the two scales. However, the fact that scores on the individual global measures of depression and sadness were more highly correlated with scores on the dementia mood scale than with the Hamilton scale scores suggests that the newer scale

TABLE 3. Significant Correlations[a] Between 21 Dementia Patients' Scores on Dementia Mood Assessment Scale Items and on Global Measures

Dementia Mood Assessment Scale Item	Correlation							
	Depression	Sadness	Functional Impairment	Cognitive Impairment	Psychosis	Mania	Anxiety	Anger
Mood subscale (17-item scale)								
1. Motor activity		0.37	0.51	0.63				
6. Irritability					0.41	0.38		
7. Agitation					0.45		0.61	
8. Anxiety							0.76	
9. Depressed appearance	0.69	0.71						
11. Responsiveness	0.40	0.43						
12. Enjoyment	0.63	0.60						
13. Self-esteem	0.65	0.43						
14. Guilt feelings	0.47	0.50						
15. Hopelessness	0.75	0.57						
16. Suicidality	0.44	0.41						
Total on 17-item scale	0.73	0.65						
Severity subscale (items 18–24)								
19. Paranoia				0.46		0.49		0.38
20. Psychotic symptoms					0.65	0.45		
21. Expressive skills			0.54	0.39				
22. Receptive skills			0.42	0.48				
Total on items 18–24			0.49	0.46				

[a]Correlations are given only if $r>0.35$ and $p<0.002$.

may better reflect underlying mood in this dementia population. This finding is all the more interesting in light of the relatively narrow range of severity of dementia in these subjects and the exclusion from the study of all other diagnostic categories that could have broadened the range of Dementia Mood Assessment Scale scores and perhaps increased the interrater correlations considerably. (When Dementia Mood Assessment Scale scores of a limited number of normal control subjects and elderly depressed patients were added to the ICC analysis, the coefficient did increase substantially.)

The considerable agreement on dementia mood scale and global ratings among multiple observers suggests that these measures are reliable, at least in our research setting. It is possible that the reliability coefficients for the dementia mood scale were inflated because of communication among the staff members before the interviews. Indeed, if there was a "halo effect," it might be expected to have appeared within the group of noncore raters, who generally had much more daily contact with the patients, yet there were no differences in the correlations within the groups of core and noncore raters. Nonetheless, it should be acknowledged that the interrater reliability figures are probably somewhat higher than those which would have been achieved with completely independent observers.

The 17-item dementia mood scale score was not related to global scores on either functional or cognitive impairment, suggesting that this subscale score was not simply another measure of the severity of dementia. In an earlier study that used three measures of depression (Hamilton score, Beck inventory score, and an adjective checklist), Miller (6) noted the absence of a significant correlation between depression and severity of cognitive dysfunction, which again points to a possible dissociation of these two parameters in dementia patients. Moreover, the total score on the last seven items of the dementia mood scale, which were meant to help establish the degree of dementia, was indeed correlated with both of the global impairment scores.

Other scales have recently been introduced to assess mood and behavior in dementia patients. These include the Cornell Scale of Depression in Dementia (21) and the Depressive Signs Scale (22). Of these scales, only the Cornell scale, a 19-item instrument based on brief interviews with the patient and a relative, has been validated against independent global measures of depression and has been shown to have significant interrater reliability. The Dementia Mood Assessment Scale also measures mood and behavior in the demented patient but differs from these other scales in that it is based on an interview with the patient as well as direct observation of the patient over time. It is the combination of interview and objectively observed data that makes this scale unique and perhaps more accurate. The Alzheimer's Disease Assessment Scale

(23) and the Global Deterioration Scale (16) are more general rating instruments for Alzheimer's disease; they include depressive symptom evaluation, but only on a very limited basis.

Older scales originally developed for nondemented populations may have potential usefulness but are thus far not validated for measuring mood in Alzheimer's disease. These other scales include the Brief Psychiatric Rating Scale (24, 25), the Sandoz Clinical Assessment–Geriatric (26, 27), the Nurses' Observation Scale for Inpatient Evaluation (28), the Beck Depression Inventory (29), and the Geriatric Depression Screening Scale (30). Because the last two scales are self-report instruments, they are probably less appropriate for dementia patients. As noted earlier, the Hamilton depression scale has previously been used to measure mood in dementia patients (6, 8) but has yet to be tested for validity or reliability in this population.

In conclusion, the Dementia Mood Assessment Scale appears to be a practical tool for assessing mood in dementia patients. It is based on clinical observations and earlier rating scales that were designed to measure depression in nondemented subjects. It is not intended to be used in the diagnosis of depression but rather to reflect the severity of mood disturbance in this cognitively impaired population. As a rating instrument, it has potential usefulness for monitoring mood changes longitudinally or monitoring them under drug treatment conditions. It could also conceivably be used for evaluating patients with other diagnoses whose cognitive impairments may hinder the clinical measurement of depressive features. However, test-retest reliability and sensitivity to change over time within individuals must first be established. These and other follow-up studies are currently under way.

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Anxiety Disorders in Mid-Adolescence: A Community Sample

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The authors report the 6-month period prevalence of anxiety disorders in a community sample of 150 adolescents 14 to 16 years old. Diagnoses were based on structured psychiatric interviews, DSM-III *criteria, and a psychiatrist's review of the data. Additional measures of affect, self-concept, and coping were also obtained for all subjects. Seventeen percent of the adolescents met criteria for one or more anxiety diagnoses and 8.7% were identified as "cases" of anxiety disorder. A significant relationship was found between anxiety and depression. The authors discuss the distribution and expression of anxiety disorders among adolescents in the community.*

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During the past decade, few studies have focused on the population prevalence of specific child and adolescent psychiatric disorders (1–3). True estimates of prevalence can be obtained only by determining the extent to which a disorder is present in the population at risk. Estimates of rates from treated populations are biased by such factors as the patients' socioeconomic status and the availability of services in a community. Because of referral biases, rates based only on treated cases may in fact represent only the most severely ill or disabled individuals, may provide inaccurate sex ratio estimates, and may reflect distorted expressions of a given disorder (4). Therefore, data from epidemiologic studies are essential for providing accurate information on the distribution of disorders and their associated risk factors and for service planning needs.

A review of child psychiatric epidemiologic research in the United States (5) showed that most studies reported global estimates of maladjustment rather than estimates of specific disorders. A more recent review of the literature (6) indicated that no epidemiologic data were available on specific anxiety disorders in children and adolescents and that existing data were limited to symptom prevalence estimates. These studies (7–11) did report that anxiety symptoms were more frequent in girls than boys and provided symptom prevalence estimates that ranged from 8% to 36% for boys and 17% to 50% for girls. However, all the available studies differed in the age groups studied, the informants used, the type and method of assessment, and the definition of "caseness." These early studies of anxiety generally predated the availability of *DSM-III* criteria and the more recent advances in structured psychiatric interviews suitable for use with children and adolescents (12). However, studies of anxiety among clinically referred children (13–15) and children of parents with affective disorder (16) have been reported more recently.

In this paper we will report the 6-month period prevalence of anxiety disorders in a community sample of systematically selected adolescents. Diagnostic assessments were based on direct interviews with adolescents using a well-established and reliable structured interview. Diagnoses were made according to *DSM-III* criteria, and all the interview material was additionally reviewed by a child psychiatrist (J.H.K.) who evaluated the clinical significance of the reported symptoms. In addition to a structured psychiatric interview, subjects provided information on their perceptions of their own affect, their self-concepts, and their coping styles so that the diagnostic assessments could be compared with these alternative measures of behavior. We hope that these epidemiologic data on adolescent anxiety disorders will provide a more veridical picture of the expression of this diagnostic category, its distribution in the population, and its association with other forms of behavioral disturbance.

METHOD

Subjects

The participants in this study were 150 adolescents (75 girls, 75 boys) who were 14, 15, or 16 years old (50 in each age group). Subjects' names were system-

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atically drawn from a population of 1,703 students on school lists in a Midwestern public school system to obtain equal numbers in each age group. (A systematic sampling draws every nth case from a population [17].) To maintain group homogeneity, we selected only those 14-, 15-, and 16-year-olds whose age would not change during the 5-month data collection phase of the study. This resulted in a final tally of 262 14-year-olds, 485 15-year-olds, and 251 16-year-olds for possible participation in the study. Based on our study design, to have participation from 50 individuals in each age group and allowing for refusals, we selected every third name of 262 14-year-olds, every fourth name of 485 15-year-olds, and every other name of 251 16-year-olds to be contacted by telephone for possible participation in the study. (The U.S. census estimated that 4% of the households in this community sample would not have a phone.)

The participating adolescents and their parents provided written informed consent and were paid $20. The only information that we could obtain from families who refused to participate was their socioeconomic status, provided by 41 of these 59 individuals. The mean socioeconomic status for the 41 people who refused to participate in the study was 3.0, compared with 2.8 for the 150 participants. The proportion of the subjects who refused to participate who were in socioeconomic class I or II was 29% (N=12); the proportion of the participants who were in class I or II was 42% (N=63) (χ^2=1.69, df=1, n.s., chi-square with Yates' correction).

Ninety-five percent (N=142) of the participating subjects were white, 4% (N=6) were black, and 1% (N=2) were Oriental; the catchment area is 90% white, 8% black, 1% Oriental, and 1% Hispanic. There were no Hispanics in the sample. The socioeconomic status of the adolescents, based on the Hollingshead and Redlich two-factor index of social position (18), was as follows: 16 (11%) were in class I, 47 (31%) were in class II, 44 (29%) were in class III, 41 (27%) were in class IV, and two (1%) were in class V.

Interview Procedure

Subject participation was solicited by telephone. For each consenting subject, information was collected during a home interview and by means of a mail-in questionnaire. During the home visit, both the child and the parent were interviewed separately through structured interviews (the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents—Parent Version, respectively) (19). Interviews were conducted by one of three master's-degree-level clinicians, all of whom were Ph.D. candidates in psychology. The three interviewers underwent an extensive training program in the administration of the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents—Parent Version before the study (1). Each conducted several interviews while being videotaped; the videotape was then reviewed by the other two clinicians as well as by the investigators. Interrater reliability training was accomplished by having the interviewers fill out the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents—Parent Version while observing the videotaped interviews of the other interviewer. We required at least 95% agreement among the interviewers on individual items before the actual study began. In addition, for the first 20 subjects, each interviewing clinician was observed by one of the other two clinicians, who also recorded the subject's responses. Ongoing supervision of interviewers was continued throughout the study, and retraining exercises were conducted after each 30–50 interviews, thus minimizing rater drift.

Assessments

Information on symptoms and psychopathology was obtained with the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents—Parent Version. These structured psychiatric interviews are administered directly either to the adolescent (the Diagnostic Interview for Children and Adolescents) or to the parent (the Diagnostic Interview for Children and Adolescents—Parent Version) and are designed to assess psychopathology according to *DSM-III* criteria. Data on the use of the Diagnostic Interview for Children and Adolescents and its psychometric properties have been reported elsewhere (12, 19, 20). In this study, diagnostic decisions were based on information obtained from the adolescent; this decision was based on previously reported findings that children are better informants of their own internal states (21) and that diagnostic reliability increases with the age of the child (22). Information provided by the Diagnostic Interview for Children and Adolescents—Parent Version was used as an independent source by the psychiatrist to assess the presence and/or degree of impaired functioning and the need for treatment.

Additional measures available for this sample included three self-administered paper and pencil inventories. They were the Multiple Affect Adjective Checklist (23, 24), the Piers-Harris Children's Self-Concept Scale (25), and the Ways of Coping Scale (26). These measures were included as alternate or validating indices of psychopathology and affect, as well as for the provision of data on adolescents' behavioral and personality attributes.

The Multiple Affect Adjective Checklist is a 132-item inventory designed to assess the adolescent's perception of his or her affective state. The instrument rates three negative affect subscales (anxiety, depression, and hostility) and two positive affect subscales (positive affect and sensation seeking). Low scores on the Multiple Affect Adjective Checklist indicate positive affect. In this study we administered the trait ver-

sion of the instrument, which is designed to measure more stable attitudes and self-perceptions.

The Piers-Harris scale is an 80-item forced-choice measure designed to assess the adolescent's self-concept on the following six dimensions: behavior, intellectual and school status, physical appearance and attributes, anxiety, popularity and happiness, and satisfaction. High scores are indicative of high self-esteem.

The Ways of Coping Scale assesses the methods of behaviors individuals use to cope with a stressful situation. The instrument first requires that the individual describe his or her most stressful event or situation during the past month. This is followed by 54 statements listing possible ways of dealing with the stressful event. The adolescent then rates, on a scale of 1–5, the degree to which he or she agrees with each statement. A principal component analysis with a varimax rotation of this measure resulted in a five-factor solution, accounting for 41% of the variance. The five factors, named according to the items that loaded on them, are fantasy-displacement, guilt-action, optimism-growth, opportunistic-inspirational, and interpersonal advice seeking.

Criteria for Identifying Cases

A structured diagnostic interview was used to determine whether a subject met criteria for a disorder. Since the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents—Parent Version do not have sections for assessing impaired functioning or the need for treatment in general, a scale was developed to rate both the degree of dysfunction and the need for treatment, based on the results of the diagnostic interview. The rating scale comprised four categories: 1) healthy—no need for treatment; 2) mildly impaired—might benefit from treatment; 3) moderately impaired—definite need for treatment; 4) severely impaired—serious need for treatment.

The above procedure thus helped to identify subjects as "cases," defined as meeting the criteria for a disorder, and to assess the presence of impairment (rating of 3 or more) requiring treatment. After completing the structured interview, the clinicians recorded a judgment regarding the subject's diagnosis and need for treatment. In addition, a child psychiatrist reviewed all available symptom information and made an independent judgment on diagnosis and the need for treatment. A subject was established as a "case" only when both the clinician and the psychiatrist were in agreement on both these established criteria.

RESULTS

Prevalence and Characteristics of Anxiety

Twenty-six adolescents (17.3% of the sample) reported a sufficient number of anxiety symptoms on the Diagnostic Interview for Children and Adolescents to meet criteria for at least one anxiety diagnosis. Thirteen of these 26 adolescents (8.7% of the sample) were identified as anxiety disorder cases according to *DSM-III* criteria and clinically significant functional impairment requiring intervention. Of the 13 anxiety cases, 11 met criteria for overanxious disorder, seven for phobic disorder, one for separation anxiety disorder, and none for obsessive-compulsive disorder. One adolescent met criteria for all three diagnoses (overanxious disorder, phobic disorder, and separation anxiety disorder), and an additional four met criteria for two diagnoses (overanxious disorder and phobic disorder). The remaining eight subjects met criteria for only one anxiety diagnosis, mostly overanxious disorder.

Table 1 shows the 6-month period prevalence of anxiety according to adolescents' demographic characteristics. The number of anxiety cases and symptoms remained fairly stable over time during the middle adolescent period studied. Also, no differences in socioeconomic status were found between the anxious and nonanxious subjects. A significantly lower prevalence of anxiety diagnoses was found among white than among nonwhite adolescents but no significant race differences were found for anxiety cases.

Comorbidity of Anxiety and Depression

Most adolescents who met criteria for anxiety were noted to have at least one additional concurrent nonanxiety diagnosis. Of the 26 anxious and 12 depressed adolescents, nine were both anxious and depressed.

This comorbidity of anxiety and depression was associated with "caseness." Of the 28 cases, nine had both anxiety and depression; conversely, all of the nine subjects with comorbidity were cases.

Girls were more likely than boys to be identified as cases (relative risk based on odds ratios for girls was 1.76:1.00 for anxiety and 2.03:1.00 for depression) irrespective of type of diagnosis or presence of comorbidity.

Self-Administered Inventories

The data from the three paper and pencil checklists (the Multiple Affect Adjective Checklist, the Piers-Harris scale, and the Ways of Coping Scale) were analyzed to determine whether anxious adolescents differed from adolescents without anxiety in how they perceived their own behavior. Two-tailed t tests were used to determine significant differences between groups.

The Multiple Affect Adjective Checklist assesses the adolescent's perception of his or her affective state and provides subscale scores for anxiety, depression, hostility, positive affect, and sensation seeking. Anxious adolescents reported significantly more mean±SD anxiety (56.3±9.6 compared with 48.0±8.1; $t=4.56$, $df=148$, $p<0.0001$) and hostility (54.3±13.0 compared with 49.1±9.4; $t=2.36$, $df=148$, $p<0.02$) than

TABLE 1. Demographic Characteristics of Adolescents With at Least One Anxiety Diagnosis and Adolescents Identified as Cases of Anxiety Disorder in a Community Sample[a]

Characteristic	Total Sample	Subjects With Anxiety Diagnosis						Subjects Identified as Cases					
		N	%	95% Confidence Interval[b]	Analysis[c] χ^2	df	p	N	%	95% Confidence Interval[b]	Analysis[c] χ^2	df	p
Sex					2.28	1	0.13				3.03	1	0.08
Male	75	9	12	6-22				3	4	1-12			
Female	75	17	23	14-34				10	13	7-24			
Age (years)					1.49	2	0.48				0.17	2	0.92
14	50	6	12	5-25				4	8	3-20			
15	50	10	20	10-34				5	10	4-23			
16	50	10	20	10-34				4	8	3-20			
Socioeconomic status (class)					0.03	1	0.85				0.32	1	0.57
I or II	63	10	16	8-28				4	6	2-16			
III, IV, or V	87	16	18	11-28				9	10	5-19			
Total	150	26	17	12-25				13	9	5-15			

[a]Figures for race are not given because the marginal total for nonwhite subjects was small. The difference between white and nonwhite subjects with an anxiety diagnosis was significant (p=0.03, Fisher's exact test); the difference between white and nonwhite subjects identified as cases was not.
[b]Confidence intervals are from Fleiss (27).
[c]Eight tests of significance at the 0.05 level were run; one was significant. The Bonferroni significance criterion for eight tests is 0.006. The two-by-two chi-squares were continuity adjusted.

did the nonanxious adolescents. The Piers-Harris scale provided similar findings, except that only the dimension of anxiety significantly differentiated anxious from nonanxious subjects (on this scale, a low score indicates greater anxiety): 6.8±2.8 compared with 8.6±2.5; t=3.24, df=148, p<0.002. In addition, anxious cases reported significantly more concern about their behavior than did the remaining sample: 12.3±3.2 compared with 14.7±3.8; t=2.18, df=148, p=0.03.

As mentioned before, the Ways of Coping Scale was factor analyzed and yielded five factors: fantasy-displacement, guilt-action, optimism-growth, opportunistic-inspirational, and interpersonal advice seeking. Anxious adolescents were significantly more likely to deal with stressful events by using fantasy, wishful thinking, denial, and displacement (factor 1) than were nonanxious adolescents (t=2.17, df=141, p<0.03). This was true for both anxious cases and noncases. None of the other four factors differentiated the anxious from the nonanxious group.

DISCUSSION

The adolescents in this study were a nonreferred systematic sample, representative of students 14 to 16 years of age, attending public schools in a Midwestern town. A little over 17% of the adolescents in this community study met criteria for one or more anxiety diagnoses, and 8.7% of the sample were considered sufficiently impaired by their symptoms to be identified as anxiety cases. Significantly more girls than boys met criteria as cases.

The most frequently occurring anxiety diagnosis in this adolescent sample was overanxious disorder; the least frequent were separation anxiety disorder and obsessive-compulsive disorder. This is in contrast to data reported for preadolescents (2) showing that the most frequently occurring diagnosis was separation anxiety disorder and the least frequent, overanxious disorder. A comparison of these two cross-sectional epidemiologic studies may suggest developmental differences in the prevalence of specific types of anxiety disorders. However, the preadolescent study not only used a different structured interview but also modified and shortened that interview to suit the setting. Therefore, a prospective population study using the same structured interview in different age groups could provide more definitive data on the validity of a relationship between age and the expression of anxiety.

The findings of this study indicate that anxiety disorders are the most common type of psychiatric disorders for adolescents, with or without consideration for "caseness." This is consistent with the findings of Myers et al. (28), who also found that the most common psychiatric disorder in adults from the general population is anxiety disorder (phobia). Since there is no U.S. study available on the prevalence of anxiety disorders in children from the general population, future studies will have to determine if an anxiety disorder is the most common type of psychiatric disorder in children as well.

The inventory measures of affect used in this study indicated that subjects were consistent in their reporting of anxiety. Adolescents with a Diagnostic Interview for Children and Adolescents diagnosis of anxiety scored significantly higher on the anxiety subscales of both the Multiple Affect Adjective Checklist and the Piers-Harris scale than did the adolescents without an anxiety diagnosis. On the Ways of Coping Scale, anxious adolescents were more likely to cope with stress by using fantasy than were the nonanxious adolescents.

Finally, differences in the anxiety subscale scores on

the Multiple Affect Adjective Checklist and the Piers-Harris scale were even more pronounced when the scores of only anxiety cases were considered. This suggests that case status was generally a function of severity and that this severity was quantifiable on the paper and pencil measures. In effect, anxiety cases and noncases differed quantitatively but did not differ qualitatively from each other but did differ in both respects from the nonanxious sample in their self-perceptions of affect and their coping strategies, as measured on the self-report inventories used in this study.

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Predictors of Violence in Civilly Committed Acute Psychiatric Patients

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The authors investigated the relationship between community violence and violence in the hospital for patients hospitalized through emergency civil commitment. The medical charts of 238 patients involuntarily admitted to a university-based acute inpatient unit were reviewed for evidence of violence during the 2 weeks before commitment and the first 72 hours of hospitalization. Patients who were violent in the community were more likely to be violent in the hospital. A discriminant function analysis was used to identify the combination of information concerning community violence and patient background characteristics that most efficiently predicted which patients were violent during emergency commitment.

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Although mental health professionals must frequently make evaluations of dangerousness, these evaluations are often inaccurate (1). Accurate assessment of dangerousness is particularly important in the case of patients who are hospitalized involuntarily for emergency psychiatric evaluation. As a group, patients hospitalized by means of emergency involuntary commitment have a high rate of violence, both before and after admission to the hospital (2–4). Accurate evaluations of dangerousness are important in planning treatment interventions to prevent injury and in deciding whether to release patients or to petition for longer periods of involuntary treatment.

Unfortunately, there are few available empirical data concerning which factors have valid predictive relationships with violence in the emergency civil commitment situation. For example, recent violent behavior is widely believed by courts and clinicians to indicate the probability of future violence. However, the relationship between community assaultiveness and violence in the hospital is unclear (5, 6). Studies of criminally committed patients (7) and civilly committed patients in Veterans Administration hospitals (8) suggest that different factors may be related to assault in the community and assault in the hospital. Monahan (9) has suggested that predictions of violence could be improved by incorporating actuarial methods into the prediction process. Development of such statistical data for short-term civil commitment requires establishing the variables that have valid predictive relationships with violence in this context.

In this study we investigated the relationship between preadmission violence and violence in the hospital during the emergency civil commitments of a heterogeneous group of community mental health center patients. Three specific questions were addressed: 1) Are patients committed after recent overt acts of violence more likely to engage in violent behavior during the first 72 hours of commitment than patients who have not engaged in recent violent behavior? 2) Are the patient characteristics associated with violent behavior in the community preceding emergency civil commitment different from the patient characteristics associated with violent behavior in the hospital during the commitment? and 3) What is the most efficient combination of information concerning preadmission violence and background patient characteristics for predicting which patients will be violent during emergency commitment?

METHOD

The setting was a university-based locked short-term treatment unit that provides inpatient psychiatric services for an urban, middle-class catchment area of approximately 200,000 people. The potential subjects included all patients admitted during the first 6 months of 1984 (N=118) and 150 patients randomly selected from admissions during 1983. After removal of the voluntary admissions and data from the later hospitalizations of patients with multiple admissions, a total of 238 unduplicated involuntary patients were retained for study. Each subject had been hospitalized with a

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72-hour emergency civil commitment, which was initiated at the time of admission after a clinician determined that the patient was a danger to others, a danger to self, and/or gravely disabled, i.e., unable to obtain food, shelter, and clothing because of mental illness (California Welfare and Institutions Code, section 5150). Of these 238 subjects, 42% had been committed because of danger to others (often with the additional grounds of danger to self and/or grave disability); the remaining 58% had been committed because they were dangerous to themselves and/or gravely disabled.

The medical record of each patient was reviewed for evidence of violent behavior during two separate time periods: 1) the 2 weeks preceding the admission and 2) the first 3 days after the beginning of the 72-hour emergency commitment. Violent behavior was rated according to an adaptation of the scale developed by Lagos et al. (10). The revised scale consists of four categories of violent behavior: attacks on persons, attacks on objects, threats to attack persons, and verbal attacks on persons. If a given record indicated that more than one of the four types of violence had occurred, only the most serious type was tabulated. The charts were reviewed by six experienced clinical staff who had been trained in the rating system to a criterion interrater agreement (11) of kappa=0.80. In addition to ratings of violence, the charts were reviewed for demographic information, legal status, the extent of suicidal behavior within the 2 weeks before admission according to an unpublished scale of Hargreaves, LeGoullen, and Gaynor (1983), and the presence or absence of a history of drug or alcohol abuse.

RESULTS

Association Between Community and Hospital Violence

The ratings of violent behavior in the community within the 2 weeks preceding emergency civil commitment showed that 53 (22.3%) of the patients had engaged in attacks on persons, 26 (10.9%) in attacks on objects, 28 (11.8%) in threats to attack persons, nine (3.8%) in verbal attacks on persons, and 122 (51.3%) in no violent behavior. During the 3 days of the emergency commitment, 43 (18.1%) of the patients engaged in attacks on persons, 32 (13.4%) in attacks on objects, 31 (13.0%) in threats to attack persons, 32 (13.4%) in verbal attacks on persons, and 100 (42.0%) in no violent behavior.

For purposes of data analysis, the four types of violence rated by the Lagos et al. scale were combined into three levels of increasingly severe violent behavior: 1) no violence, 2) fear-inducing behavior (verbal attacks on persons, threats to attack persons, and attacks on objects), and 3) physical attacks on persons. As shown in table 1, there was a significant positive association between violent behavior in the community during the 2 weeks before emergency civil commitment and violent behavior during the 72-hour commitment.

TABLE 1. Relationship Between Preadmission Violence in the Community and Violence in the Hospital During 72-Hour Emergency Civil Commitment of 238 Patients[a]

Level of Violence in the Hospital	Level of Violence in the Community: No Violence (N=122)		Fear-Inducing Behavior (N=63)		Physical Attacks (N=53)	
	N	%	N	%	N	%
No violence	72	59.0	15	23.8	13	24.5
Fear-inducing behavior	38	31.1	32	50.8	25	47.2
Physical attacks	12	9.8	16	25.4	15	28.3

[a] $\chi^2=31.66$, df=4, $p<0.0001$.

Patient Characteristics Associated With Violence

To evaluate whether the patient characteristics associated with violence in the community and violence in the hospital were different, nine variables were selected on the basis of previous research concerning demographic variables associated with violence (1, 12, 13) (see table 2). No significant bivariate associations were found between violence and social class, ethnic group, residence with family, or history of substance abuse, regardless of whether the community or hospital setting was examined. In both the community and the hospital, suicidal patients were less likely than nonsuicidal patients to be violent, and single patients were overrepresented in the group exhibiting fear-inducing behavior, whereas married patients were overrepresented in the physically assaultive group. Thus, for seven out of nine background characteristics, the relationship between the characteristic and violence was similar regardless of whether the patient was in the community or in the hospital. This suggests considerable consistency across situations in the characteristics associated with violence in this acutely ill sample.

Nevertheless, situational factors do appear to moderate the relationship between violence and some patient characteristics. Men were more likely than women to engage in fear-inducing behavior and physical attacks on others in the community. In the hospital, men continued to be overrepresented in the group of patients exhibiting fear-inducing behavior, whereas women were overrepresented in the physically assaultive group. In addition, both schizophrenic and manic patients were overrepresented in the group who were physically assaultive in the community, but manic patients were most likely to be physically assaultive in the hospital. Since the distribution of diagnostic categories differed by gender, we repeated the latter analyses separately for men and women. Among men, but not women, schizophrenic and manic patients were significantly more likely to engage in preadmission violence than patients with other diagnoses ($\chi^2=16.1$, df=4,

TABLE 2. Characteristics of 238 Civilly Committed Patients by Presence or Absence of Violent Behavior in the Community and in the Hospital

		Violence in the Community						Violence in the Hospital					
		No Violence		Fear-Inducing Behavior		Physical Attacks		No Violence		Fear-Inducing Behavior		Physical Attacks	
Variable	N	N	%	N	%	N	%	N	%	N	%	N	%
Sex[a]													
Male	122	42	34.4	48	39.3	32	26.2	45	36.9	60	49.2	17	13.9
Female	116	80	69.0	15	12.9	21	18.1	55	47.4	35	30.2	26	22.4
Social class													
II	4	3	75.0	0	0.0	1	25.0	3	75.0	1	25.0	0	0.0
III	10	8	80.0	1	10.0	1	10.0	2	20.0	5	50.0	3	30.0
IV	55	30	54.5	16	29.1	9	16.4	25	45.5	15	27.3	15	27.3
V	169	81	47.9	46	27.2	42	24.9	70	41.4	74	43.8	25	14.8
Marital status[b]													
Single, divorced, or widowed	198	98	49.5	60	30.3	40	20.2	84	42.4	84	42.4	30	15.2
Married or living together	40	24	60.0	3	7.5	13	32.5	16	40.0	11	27.5	13	32.5
Ethnic group													
Black	31	10	32.3	13	41.9	8	25.8	11	35.5	13	41.9	7	22.6
Caucasian	136	79	58.1	30	22.1	27	19.9	59	43.4	53	39.0	24	17.6
Asian	43	21	48.8	13	30.2	9	20.9	19	44.2	17	39.5	7	16.3
Other	28	12	42.9	7	25.0	9	32.1	11	39.3	12	42.9	5	17.9
Age (years)													
18–29	77	35	45.5	25	32.5	17	22.1	32	41.6	31	40.3	14	18.2
30–39	79	41	51.9	22	27.8	16	20.3	34	43.0	33	41.8	12	15.2
40–49	35	15	42.9	12	34.3	8	22.9	14	40.0	15	42.9	6	17.1
≥50	47	31	66.0	4	8.5	12	25.5	20	42.6	16	34.0	11	23.4
Residence													
With family	120	57	47.5	31	25.8	32	26.7	46	38.3	51	42.5	23	19.2
Other	118	65	55.1	32	27.1	21	17.8	54	45.8	44	37.3	20	16.9
Diagnosis[c]													
Schizophrenia	83	28	33.7	32	38.6	23	27.7	31	37.3	39	47.0	13	15.7
Mania	43	18	41.9	11	25.6	14	32.6	12	27.9	18	41.9	13	30.2
Other	112	76	67.9	20	17.9	16	14.3	57	50.9	38	33.9	17	15.2
Suicidal behavior[d]													
None	149	63	42.3	43	28.8	43	28.9	54	36.2	64	43.0	31	20.8
Threat	57	32	56.1	16	28.1	9	15.8	24	42.1	26	45.6	7	12.3
Gesture	20	15	75.0	4	20.0	1	5.0	13	65.0	3	15.0	4	20.0
Attempt	12	12	100.0	0	0.0	0	0.0	9	75.0	2	16.7	1	8.3
Substance abuse													
Absent	180	97	53.9	41	22.8	42	23.3	79	43.9	71	39.4	30	16.7
Present	58	25	43.1	22	37.9	11	19.0	21	36.2	24	41.4	13	22.4

[a] Community: $\chi^2=31.3$, df=2, $p<0.0001$; hospital: $\chi^2=9.32$, df=2, $p<0.01$.
[b] Community: $\chi^2=9.51$, df=2, $p<0.01$; hospital: $\chi^2=7.45$, df=2, $p<0.03$.
[c] Community: $\chi^2=25.82$, df=4, $p<0.0001$; hospital: $\chi^2=10.96$, df=4, $p<0.03$.
[d] Community: $\chi^2=23.57$, df=6, $p<0.001$; hospital: $\chi^2=14.69$, df=6, $p<0.03$.

$p<0.003$). When the patients were stratified by gender, no significant differences were found in the rates of inpatient violence among the different diagnostic groups. However, the small expected cell frequencies could explain this negative finding, as the trend for manic patients to be overrepresented in the group that was physically assaultive in the hospital was present for both men and women.

Statistical Prediction of Violence in the Hospital

A direct discriminant function analysis was performed to select the weighted combination of patient variables that could best classify which patients engaged in no violence, in fear-inducing behavior, or in physical attacks in the hospital. The 11 patient variables included in the discriminant function analysis consisted of all the variables listed in table 2 (presence or absence of a schizophrenic diagnosis and presence or absence of a manic diagnosis were included as separate variables) and whether the patient had engaged in no violence, in fear-inducing behavior, or in physical attacks in the community before admission. Bayesian adjustments were made for prior probabilities (14). Two discriminant functions were calculated with a combined Wilks' lambda of 0.78 ($\chi^2=56.44$, df=22, $p<0.0001$). The variable that contributed most to the separation of patients who engaged in no violence, in fear-inducing behavior, or in physical attacks in the hospital was whether the patient had engaged in physical attacks, fear-inducing behavior, or no violence before admission.

TABLE 3. Classification Results of Discriminant Function Analysis for Violent Behavior During 72-Hour Emergency Commitment of 238 Patients[a]

Actual Level of Violence	Predicted Level of Violence: No Violence (N=116) N	%	Fear-Inducing Behavior (N=100)[b] N	%	Physical Attacks (N=22)[c] N	%
No violence (N=100)	65	56.0	31	31.0	4	18.2
Fear-inducing behavior (N=95)	35	30.2	52	52.0	8	36.4
Physical attacks (N=43)	16	13.8	17	17.0	10	45.5

[a]Total correctly classified=53.4%.
[b]For fear-inducing behavior, true positive rate=52/100=52.0%, false positive rate=(31+17)/100=48.0%, base rate=95/238=39.9%, percent improvement over chance (true positive rate minus base rate)=52.0−39.9=12.1%, sensitivity=52/95=54.7%.
[c]For physical attacks, true positive rate=10/22=45.5%, false positive rate=(4+8)/22=54.5%, base rate=43/238=18.1%, percent improvement over chance=45.5−18.1=27.4%, sensitivity=10/43=23.3%.

To evaluate the statistical model, we employed a widely used framework (1) for analyzing the outcome of predictions. A true positive is a prediction of violence that turns out to be correct, a true negative is a prediction of nonviolence that turns out to be correct, a false positive is a prediction that violence will occur which turns out to be incorrect, and a false negative is a prediction of nonviolence for a person who actually becomes violent. The base rate of violence is the proportion of patients who become violent in a given time period; in the present study, 18.1% of the patients physically attacked others during the 3 days of emergency commitment, so the base rate of physical attacks was 18.1%. The percentage of improvement over chance refers to the difference between the percentage of true positive predictions and the base rate. Sensitivity refers to the proportion of violent patients who were accurately predicted to be violent.

The discriminant functions based on the 11 background variables correctly classified 53.4% of the patients as to whether they would engage in no violence, in fear-inducing behavior, or in physical attacks on others in the hospital (see table 3). The statistical model resulted in a 27.4% improvement over chance in classifying patients who would engage in physical attacks (i.e., the 45.5% true positive rate is 27.4% greater than the 18.1% base rate of physical attacks among the patients).

To assess the stability of the prediction equation, we conducted a cross-validation analysis. After withholding half of the cases on a randomized basis, we recomputed the discriminant function analysis. When we applied the resulting discriminant functions to the half of the sample from which the equations were derived, 63.9% of the patients were correctly classified as engaging in no violence, in fear-inducing behavior, or in physical attacks. Predictions of physical attacks had a true positive rate of 77.8% and a false positive rate of 22.2%. As expected on statistical grounds, classification accuracy decreased when we applied the prediction equation to the other half of the sample. The prediction equation correctly classified 49.1% of the remaining cases. The decrease in classification accuracy in the cross-validation sample was due primarily to several patients who were predicted to engage in fear-inducing behavior but actually physically attacked others. Predictions of physical attacks had a true positive rate of 50.0% and a false positive rate of 50.0%. This still represents a 25.9% improvement over what would be expected on the basis of chance (i.e., the true positive rate of 50.0% is 25.9% greater than the 24.1% base rate of physical attacks among patients used in the cross-validation sample). In summary, the cross-validation analysis suggests that these discriminant functions have a reasonable degree of stability and are helpful in classifying patients who are and are not violent.

To evaluate the robustness of the model across statistical methods, we also entered the 11 variables in an ordered logit analysis (15). This method does not involve as stringent assumptions about the distributional form of the independent (predictor) variables as the discriminant function analysis. The overall percentage of patients correctly classified by using the ordered logit analysis (54.2%) was similar to the percentage from the discriminant function analysis (53.4%), as were the variables that contributed most to the separation of patients who engaged in no violence, in fear-inducing behavior, or in physical attacks in the hospital. Although the basic result of the discriminant analysis was confirmed, the logit analysis was somewhat less sensitive in identifying patients who made physical attacks than the discriminant analysis (16.3% versus 23.3%).

Comparison of Statistical and Clinical Prediction

To evaluate the utility of the statistical prediction equations, we compared the accuracy of predictions based on the discriminant function analysis with the clinical judgments of dangerousness recorded on the patients' commitment papers at the time of admission. Consistent with our previous findings (3), over three-fourths of the patients committed on the basis of danger to others engaged in some type of violence during the 72-hour emergency commitment, 26.7% engaged in physical attacks, and 51.5% exhibited fear-inducing behavior. Over 40% of the patients not judged to be dangerous to others also engaged in some type of violence; 11.7% made physical attacks, and 31.4% engaged in fear-inducing behavior.

Using physical attacks as the criterion for evaluating the accuracy of the clinical judgments of dangerousness yields a true positive rate of 26.7% (i.e., 26.7% of the patients judged to be dangerous to others did attack others), which represents an 8.6% improvement over chance (26.7% minus the base rate of 18.1%) and a sensitivity of 62.8% (62.8% of the patients who en-

gaged in physical attacks had been committed on the basis of danger to others). However, the false positive rate was 73.3% (73.3% of the patients who had been judged to be dangerous to others did not physically attack others).

Compared with the clinical judgments of dangerousness, the discriminant function analysis had a higher rate of true positive predictions of physical attacks (45.5% versus 26.7%), a lower rate of false positives (54.5% versus 73.3%), and a higher percentage of improvement over chance (27.4% versus 8.6%). On the other hand, the clinical predictions had greater sensitivity (62.8% versus 23.3%). In other words, the statistical model performed better in terms of classifying specific patients as to whether they would or would not attack others. However, by overpredicting violence, the clinical predictions identified more patients who did attack others.

It should be pointed out that if other dangerous behaviors in addition to physical attacks were included in the criteria for violence, the clinical judgments of dangerousness did not vastly overpredict violence; 77.2% of the patients committed on the basis of danger to others engaged in either fear-inducing behavior or physical attacks. Similarly, 71.3% of the patients predicted by the statistical model to exhibit either fear-inducing behavior or physical attacks did exhibit either fear-inducing behavior or physical attacks. The improvements offered by the statistical model, therefore, are most evident in increasing the proportion of accurate predictions of physical attacks.

DISCUSSION

Some (5, 16) have suggested that a patient's violent behavior in the hospital is qualitatively different from violent behavior in the community. Emphasizing the role of situational factors in violent behavior, Steadman stated, "There has yet to be an empirical demonstration of statistically significant relationships between assaultive behavior by mental patients in hospitals and in the community" (7, p. 248). Our findings suggest a different conclusion. A recent history of violent behavior in the community was significantly associated with violence during the first 72 hours of emergency civil commitment in our sample of psychiatric impatients. Although situational factors do appear to moderate the influence of some patient characteristics (e.g., diagnosis, gender), for most of the patient background characteristics, the relationship between the characteristic and violence was consistent between the community and the hospital. These findings differ from previous results indicating no relationships between violence by mental patients in hospitals and in the community (7, 8). How can this discrepancy be explained?

One factor may be that this study focused on patients who were on emergency involuntary civil commitments and compared their preadmission behavior to temporally contiguous behavior in the hospital. Steadman (7), on the other hand, compared criminal patients' behavior in the hospital to their behavior in the community after release. Naturally, patients who have received extensive treatment will not be as prone to dangerousness after release. Patients who undergo emergency civil commitment after violent acts are likely to continue to be violent in the hospital until their most acute symptoms are decreased by treatment, such as psychotropic medication.

Rofman et al. (8) also studied inpatients hospitalized by emergency civil commitment but used a long-term follow-up period in comparing preadmission violence to violence in the hospital. It is possible that the consistency of violence between the community and the hospital may only be present in the short term, because the rate of violence decreases sharply after the first few days of hospitalization (3, 8).

Most previous studies on violence by psychiatric patients have not examined the same group of acutely ill patients both in the community before emergency civil commitment and during hospitalization. Our finding that men were more violent than women in the community is consistent with the results from many previous studies (4, 10, 13, 15). Similarly, our finding that in the hospital women were more assaultive but men engaged in more fear-inducing behavior suggests a lack of consistent sex differences in the overall rate of violence among inpatients. Prior reports (17–19) have also indicated a lack of consistent gender-related differences in the rate of violence among inpatients. More generally, the absence of significant associations between several demographic variables (ethnicity, social class, age, and living situation) and violence corroborates the observations of previous investigators (4, 20) that such variables have a less consistent relation to violent behavior than clinical variables, such as diagnosis. It should be noted, however, that although most of the individual demographic variables were not predictive of violence, when considered together in the multivariate analysis the demographic variables did reliably enhance the discrimination between violent and nonviolent patients.

The finding of an inverse relationship between a recent history of suicidal behavior and violence has been observed in other studies of acutely ill inpatients (21), although chronic inpatients with histories of suicidal behavior may be at greater risk for violence in the long term (17). In our study suicidal behavior had similar relationships with violence in the community and the hospital, but the relationship between violence and diagnosis (e.g., schizophrenia versus mania) differed between the community and the hospital. A new but growing body of research (4, 22, 23) suggests that the important role of different mental disorders in determining violence is moderated by the influence of the setting.

The statistical approaches described here have promise in improving clinical predictions of violence among acutely ill civilly committed patients. That is,

classification equations such as those developed in this study may be helpful in alerting clinicians to the relative weight to attribute to various background factors in evaluating the risk that an acutely ill patient will be violent in the hospital. (Additional statistical tables are available from the authors on request.) It is likely that the identification of imminently dangerous patients could be further improved by incorporating mental status variables (24) and situational variables with actuarial descriptions of patient background characteristics such as those developed in this study. Existing microcomputer technology makes it feasible to generate at the time of admission a probability statement regarding a patient's risk of violence in the hospital, based on a weighted combination of readily available patient information. This risk assessment could provide a useful supplement to clinical judgments of dangerousness.

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Epidemiologic Evidence for Early Onset of Mental Disorders and Higher Risk of Drug Abuse in Young Adults

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Data from the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area Program, an epidemiologic survey of five communities, showed that four major disorders commonly begin in late adolescence or young adulthood. The median age at onset for anxiety disorders is 15 years; for major depressive episode, 24 years; for drug abuse or dependence, 19 years; and for alcohol abuse or dependence, 21 years. Findings also suggest that for respondents 18–30 years old, having a major depressive episode or anxiety disorder doubles the risk for later drug abuse or dependence.
(Am J Psychiatry 1988; 145:971–975)

In this paper we will examine the age at onset for depressive, anxiety, and substance use disorders and the associations between these conditions, using data from the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area Program.

Initial publications from the Epidemiologic Catchment Area Program (1–3) showed that rates of anxiety disorders, major depression, and alcohol and drug use disorders were high in subjects 18–24 years old. This finding is consistent with findings from the Isle of Wight studies (4–6), the Yale Family Study (7, 8), and others (9–11) that adolescence and early adulthood are important periods for onset of depressive illness. Previous studies of drug use among adolescents and young adults (12, 13) have also demonstrated that first use of drugs of abuse peaks in the age range 15–19 years. A survey of drug use disorders in the United States (14) found that for all drugs except heroin the contemporary user population is predominantly in the age range from adolescence to about 30 years of age.

In this paper, we will examine the previous lifetime experience of young adults 18–30 years old to determine relationships between onset of drug use disorders and onset of other psychiatric illnesses. Lifetime data from the initial wave of the Epidemiologic Catchment Area Program are retrospective in that they come from a cross-sectional study, and that makes it more difficult to establish the sequence of the onset of disorders than it would be in a prospective study. However, the ideal alternative—broad-based longitudinal studies of adolescent populations with contemporary diagnostic criteria like *DSM-III*—will not be available soon. The Epidemiologic Catchment Area Program study was limited to subjects 18 years old and older because it was felt that no suitable diagnostic instruments existed to assess adolescents in an epidemiologic survey (15).

In the absence of the desired prospective studies, the Epidemiologic Catchment Area Program data are useful because they provide at least a limited opportunity to examine age at onset and relationships among disorders in a general population (16). Examining the association between disorders in clinical populations alone may lead to misleading impressions because of "Berkson's fallacy." That term refers to the apparent overstatement of the association between two disorders if each independently leads a person to seek medical care. For that reason, associations between disorders are best studied in representative samples of general populations (17).

METHOD

The NIMH Epidemiologic Catchment Area Program was a combined community and institutional survey of at least 3,500 respondents in each of five different communities. In this paper, we are using data from the 18,572 household respondents to examine onset of four groups of disorders: major depressive episode, anxiety disorders, drug abuse or dependence, and alcohol abuse or dependence. We used the subgroup of 4,778 respondents aged 18–30 years old to examine associations between these disorders.

The diagnostic instrument developed for the Epidemiologic Catchment Area Program study was the NIMH Diagnostic Interview Schedule (DIS) (18, 19). It uses a lifetime framework for inquiring about the subjects' experiences with symptoms relevant for *DSM-III* diagnoses. For example, in inquiring about the mood disturbance that is a required criterion for major depression, the DIS interviewer asks the subject, "Have

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TABLE 1. Estimates of Prevalence and Age at Onset of Anxiety, Depression, and Drug or Alcohol Abuse in the Epidemiologic Catchment Area Program[a]

	Lifetime Diagnosis				6-Month Diagnosis			
	Prevalence		Age at Onset (years)		Prevalence		Age at Onset (years)	
Disorder	%	SE	Median	Mean	%	SE	Median	Mean
Anxiety disorders	14.6	0.4	15	19.6	8.9	0.3	15	19.8
Major depressive episode	5.8	0.3	24	25.6	3.0	0.2	24	26.3
Without mania	5.2	0.2	25	26.1	2.6	0.2	25	26.9
With mania	0.5	0.1	18	19.3	0.3	0.1	19	18.2
Drug abuse or dependence	5.9	0.2	19	20.2	2.0	0.1	18	19.5
Alcohol abuse or dependence	13.3	0.4	21	23.2	4.7	0.2	21	22.7

[a]Note: these estimates are for subjects of all ages at all five sites.

you ever experienced . . ." to set the person's entire previous lifetime as the frame of reference for the question about the symptom. If several symptoms are positive, additional questions include an inquiry about, "How old were you when you first experienced . . . ."

To be conservative in estimating the importance of childhood or adolescent onset, the 691 subjects who had a diagnosis of anxiety disorder but reported it had been present throughout their entire lifetimes were not included in calculations of percentage distribution of age at onset or of mean and median ages at onset for anxiety disorders. Because this omission leads to exclusion of some subjects reporting childhood onset, it produces an older age at onset pattern for anxiety disorders than would have been obtained if these subjects had reported a precise year of onset.

Both site-specific rates and summary rates for these disorders will be presented in this paper. The summary results have been calculated by using a set of sampling weights that weight the entire five-site sample to the 1980 census of the U.S. adult population over 18 years old on the basis of age, sex, and race or ethnicity (3). For these rates, standard errors have been estimated by using the SESUDAAN program to account for the complex survey design (20).

An odds ratio was used to estimate the higher risk of a disorder in those with a suspected risk factor. It was calculated as the odds of having the disorder for those with the suspected risk factor, divided by the odds for those without the factor. When these two odds were the same, the odds ratio was 1.0; when the odds of having the disorder were higher in those with the suspected risk factor, then the odds ratio was greater than 1.0, and its magnitude indicated the level of higher risk. Confidence intervals were calculated by a logarithmic transformation of the odds ratio and its standard error: ($\log_e$[odds ratio]$\pm$1.96 [standard error $\log_e$ odds ratio]) (21).

RESULTS

Age at Onset

For the total population studied, the median age at onset for each category of lifetime disorder ranged from 15 to 25 years; the mean age ranged from 19.3 to 26.1 years. Table 1 shows that these mean and median ages at onset for diagnoses on a lifetime basis were similar to those for 6-month diagnoses, obtained when analysis was restricted to illness that had been active in the 6 months before interview. This similarity shows that subjects with recent illnesses also reported an early age at onset, so the finding does not apply just to those who reported having had the illness at any time in the past.

Elevated Risk of Developing Drug Abuse

In the Epidemiologic Catchment Area Program, 22.3% of the 18–30-year-olds had a substance use disorder; 6.2% of the young adults had experienced both a substance use disorder and one of the depressive or anxiety disorders. Of those with multiple disorders, 80% reported onset before age 20.

This group of young adults showed an overall association between having had a major depressive episode and having had a substance use disorder, with an odds ratio of 2.7 (95% confidence interval, 2.1 to 3.2). For anxiety disorders, the odds ratio was 1.7 (95% confidence interval, 1.5 to 2.1). However, these total associations do not differentiate between depressive or anxiety disorders that came before the substance use and those which reportedly arose later, perhaps as secondary to the drug or alcohol use. For that reason, the sequence in onset of these disorders was considered, so that odds ratios could be calculated by dropping from the "risk" group anyone whose substance abuse disorder was reported to develop first, before any depressive or anxiety disorder.

To determine whether a depressive or anxiety disorder may have been related to subsequent development of a substance use disorder, the reported age at onset for each disorder was used to group these individuals into one of our patterns of onset, as shown in table 2. Almost three of every four subjects with multiple conditions had the first or second pattern, indicating that the anxiety or depressive disorder started at an earlier age than the substance use disorder (either drugs or alcohol) or the drug use disorder considered alone (table 2).

When age at onset was considered in forming the

TABLE 2. Sequence of Onset of Depression or Anxiety and Drug or Alcohol Abuse in Young Adults 18–30 Years Old in the Epidemiologic Catchment Area Program

Sequence of Onset	Lifetime Prevalence %	Lifetime Prevalence SE	Percent With Onset of First Disorder Before Age 20
Subjects with major depressive episode or anxiety disorder and drug or alcohol use disorder			
Anxiety disorder, then substance use disorder	3.4	0.3	75.0
Major depressive episode, then substance use disorder, then anxiety disorder	1.1	0.2	89.8
Substance use disorder, then anxiety disorder	0.7	0.2	90.3
Substance use disorder, then major depressive episode, then anxiety disorder	1.0	0.2	77.3
Any pattern	6.2	0.4	79.7
Any substance use disorder	22.3	0.8	72.1
Subjects with major depressive episode or anxiety disorder and drug use disorder			
Anxiety disorder, then drug use disorder	2.5	0.3	80.7
Major depressive episode, then drug use disorder	0.9	0.2	83.7
Drug use disorder, then anxiety disorder	0.5	0.2	96.5
Drug use disorder, then major depressive episode	0.7	0.1	75.8
Any pattern	4.6	0.4	82.1

TABLE 3. Odds Ratios of Developing Drug Use Disorder After Major Depression or Anxiety Disorders in Young Adults 18–30 Years Old in the Five Sites of the Epidemiologic Catchment Area Program

Site	Odds Ratio Men	Odds Ratio Women
New Haven	3.1	2.0
Baltimore	1.0	1.4
St. Louis	3.1	2.4
Durham	1.6	1.8
Los Angeles	2.3	1.8
Combined estimate for the United States	2.2	1.9

"risk group," the combined data from all five sites indicated no overall elevation in risk for a later alcohol use disorder in subjects with an early onset of depression or anxiety disorders; the odds ratio was 1.1 (95% confidence interval, 0.9 to 1.3), which is comparable to the null value of 1.0 indicating an equal risk in the two groups. For drug use disorders, the odds ratio was elevated at 2.2 (95% confidence interval, 1.8 to 3.1) for men and 1.9 (95% confidence interval, 1.4 to 2.4) for women. Site-specific odds ratios for drug use (table 3) showed higher values at New Haven, St. Louis, and Los Angeles. By contrast, at Baltimore and Durham, the two sites with notably high rates of simple phobias, the association between substance abuse and affective or anxiety disorders was diluted and the odds ratios were correspondingly lower. A reanalysis that omitted simple phobias from the anxiety disorders group showed that odds ratios for men increased from 2.2 to 2.7 (95% confidence interval, 2.0 to 3.8) in the combined data.

DISCUSSION

Age at Onset

These Epidemiologic Catchment Area Program data provide evidence from retrospective self-reports by community residents of the importance of early onset of major mental disorders, especially anxiety disorders. The common tendency for adult respondents to pinpoint very early ages, even before adolescence, for the onset of symptoms of anxiety disorders emphasizes the possible continuity of childhood anxiety disorders like separation anxiety, school avoidance and other phobic behaviors, and obsessive-compulsive disorder with similar conditions persisting into adult life.

For major depression, the data emphasize the predominance of onset in the decade from mid-adolescence to the mid-20s. Community-based studies (11, 22, 23) have discussed the importance and possible recent increase of early-onset cases, and these Epidemiologic Catchment Area Program findings are consistent with Klerman's suggestion (24) that depressive disorders may have become more common or may be occurring at earlier ages in more recent generations through the past half-century.

These findings reinforce earlier reports from more specific studies (12, 13, 25) of the importance of first drug use in mid- to late-adolescent ages for subsequent development of drug abuse and dependence.

Risk for Drug Abuse and Dependence

These findings demonstrate a doubling of risk for subsequent drug use disorders in young adults who have had an earlier depressive or anxiety disorder. For comparison, the magnitude of this elevation in risk is similar to recent reports for alcohol consumption and cancer of the breast (relative risk estimated as 1.5) (26).

This finding corroborates reports of such an elevated risk in two earlier studies. Newcomb et al. (27) showed that elevated scores on a rating scale of four depressive symptoms was one of several factors predicting later drug use in an adolescent sample. In a study based on the DIS in a college-age population, Deykin et al. (28) reported odds ratios of 3.0 to 4.0 for a history of substance abuse; they did not report odds ratios that had

been adjusted for subjects who reported that their depressive or anxiety disorders started after their substance use. Also, in clinical populations, a high rate of co-occurrence of drug use and other mental disorders has been reported (29–31), which is consistent with these findings of higher risk; however, no association between adolescent depression and later drug use in adulthood was found in another study (32).

Possible Limitations

Epidemiologic studies are subject to certain pitfalls. Four specific limitations are relevant to this report.

Two potential problems, the reliance on nonclinician interviewers and the possible reluctance of respondents to discuss illicit drug use, have been previously considered in methodologic studies. In terms of the use of nonclinicians to administer the DIS, studies have shown that test-retest agreement and comparisons with clinicians' diagnoses made by another method have been especially good for alcohol disorders, major depression, and drug use disorders (33). In fact, the most striking evidence for acceptable performance of the DIS was found in a group of patients with drug and alcohol abuse or dependence (34). In this study, the DIS was compared with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version administered by clinicians. For anxiety disorders, though, the performance of the DIS has been more variable (33, 35).

Two other potential problems apply to the age at onset findings. In terms of distribution of age at onset across ages, the general decline in lifetime prevalence with increasing age found in older subjects in the Epidemiologic Catchment Area Program is not yet understood. It may be a methodologic problem based on poor recall or reporting by older subjects or earlier mortality of those with a psychiatric disorder, or it could be a true finding (1). For the conditions considered in this analysis, the principal concern would be possible underreporting of alcohol or depressive disorders among the elderly. Such underreporting could understate the relative importance of depressive disorders or alcohol use disorders occurring in the elderly, and that would affect the estimates of median age at onset reported here. It would be less likely, however, to affect the estimates of elevated risk for subsequent drug abuse or dependence, since these risk calculations have been based only on the experience of the young adult group. More definitive estimates of lifetime risk for developing these illnesses will require longitudinal studies and information about course of illness and mortality in the risk and illness groups (36).

Another concern in a study attempting to reconstruct the course of illness in subjects from a cross-sectional survey is the accuracy of age at onset self-reports. Clinical investigators (31) have emphasized the inaccuracy of such data, but one study of how accurately adolescents report first use of drugs (37) has suggested that such reports are adequate. In a study of the time-related questions on the DIS specifically, Wittchen et al. (38) found that the reliability of age at onset data varies by disorder but generally corresponds to the reliability of the individual symptom items used to determine presence of the disorder. For most conditions the reliability of age at onset questions is generally acceptable, but for phobias in particular reliability is not adequate. This methodologic problem may explain why the odds ratios for some groups were low at the two sites with large rates of phobias and why they increased when the calculations were repeated without including simple phobias in the group of anxiety disorders. Despite the need to overcome these problems, more accurate data in a large general population sample would be difficult to obtain in a cross-sectional study like the Epidemiologic Catchment Area Program and are unlikely to be available in the near future. If reporting is more accurate for younger ages, the restriction to subjects 18–30 years old for the risk analyses in this paper may help avoid the most severe inaccuracies in dating onset and establishing course of illness.

In summary, striking evidence for onset of major disorders in adolescence or earlier has been found for respondents in the Epidemiologic Catchment Area Program. Possible underreporting of depression and alcohol disorders by the elderly may influence somewhat the distributions found for these two conditions, but for anxiety and drug use disorders the early onset finding is dramatic and appears consistent with earlier studies. Evidence of a modest but important elevation of risk for subsequent drug abuse or dependence has also been found in young adults who had earlier episodes of an anxiety or depressive disorder. Besides corroborating two other reports, this finding—combined with the prevalence estimates that demonstrate the public health burden of these illnesses—should stimulate studies of therapeutic or preventive interventions in adolescents as well as research on the underlying nature of the relationship.

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Psychiatric Disorder in a Sample of the General Population With and Without Chronic Medical Conditions

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The authors studied data on psychiatric disorders and eight chronic medical conditions in a community sample of 2,554 persons. The sex- and age-adjusted prevalence of any psychiatric disorder in the preceding 6 months was 24.7% and of lifetime psychiatric disorder was 42.2% among persons with one or more medical conditions, compared to 17.5% and 33.0%, respectively, for persons with no medical condition. Persons with chronic medical conditions were more likely to have lifetime substance use disorders and recent affective and anxiety disorders. Arthritis, cancer, lung disease, neurological disorder, heart disease, and physical handicap were strongly associated with psychiatric disorders, but hypertension and diabetes were not.

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Estimates of the prevalence of psychiatric disorders in persons with chronic medical conditions are of considerable clinical and policy interest for several reasons. First, psychiatric disorders complicate the clinical assessment of patients with chronic medical disease (and vice versa). Second, primary care physicians may not always detect psychiatric disorder in patients with medical disease (1, 2). Third, treatments for the two types of disorders (e.g., antihypertensive and antidepressant medications) may interact (3, 4). Fourth, coexisting psychiatric disorders could increase both the utilization of health services and the disability of persons with chronic medical conditions.

While earlier studies found a high prevalence of psychiatric disorder or distress in persons with chronic medical disease (5–8), these studies had one or more methodologic flaws that limited their conclusions: 1) nonrepresentative (treated) samples, 2) absence of measures of specific *DSM-III* psychiatric disorders, 3) focus on only one chronic medical condition or one psychiatric disorder, and 4) imprecise definition of the time frame for the psychiatric or medical disorder.

In this paper, we estimate the prevalence of specific psychiatric disorders among adults in a sample of the general population with and without eight common chronic medical conditions. We hypothesized that both depressive and anxiety disorders would be more prevalent among persons with any of these chronic medical conditions than among persons with none of the chronic medical conditions. A high prevalence of depressive disorder and/or symptoms of depression has previously been found among patients treated for coronary artery disease (5, 9), cancer (8), stroke and other neurological disorders (10–12), arthritis (12), and hypertension (13) and in postamputation patients (14). The evidence is inconclusive for the association of depression and diabetes (6). Previous studies have suggested that symptoms of anxiety or anxiety disorders are more common in persons who have had cancer (15, 16), arthritis (17), and cardiovascular disease (18). In addition, anxiety can induce hypertensive episodes (19, 20).

Although substance use disorders are among the most common psychiatric disorders (21), there are few studies of the prevalence of these disorders in persons with chronic medical conditions. Arguments can be presented in support of either a lower or a higher prevalence of substance use disorders among persons with medical conditions. Substance abuse could be more prevalent in persons with medical conditions either because the substance use causes or exacerbates the medical problem or because it serves as a means for coping with the medical problem (22). Alternatively, because substance abuse may exacerbate functional limitations, persons with chronic medical conditions may avoid the use of psychoactive substances.

METHOD

The data for this report are from the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area Program, a multisite general population survey of the epidemiology of psychiatric disorders and use of health services (23). In the Los Angeles part

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of the project, staged probability samples of household residents from two mental health catchment areas (East Los Angeles and Venice/Culver City) were drawn. Approximately 50% of the respondents were of Hispanic origin (mostly Mexican-American) (24). For each household, one adult was randomly selected to participate in a series of face-to-face interviews. The first wave of interviews, completed in 1982–1983, had a response rate of 68% (N=3,132). Respondents were somewhat more likely than the corresponding household population to be young and Hispanic (25). This paper reports data on all Mexican-Americans and non-Hispanic whites in the sample (N=2,554).

Data on psychiatric disorders were obtained with the NIMH Diagnostic Interview Schedule (DIS) (26), a structured interview administered by laypersons that yields diagnoses according to *DSM-III* criteria. A Spanish-language version of this instrument (27, 28) was developed specifically for this study. We developed indicator variables for the presence of any affective disorder (major depression, dysthymia, or mania), any substance use disorder (alcohol or drug abuse or dependence), any anxiety disorder (panic disorder, phobia, or obsessive-compulsive disorder), and any psychiatric disorder (any of those already mentioned plus schizophrenia/schizophreniform and somatization disorder, antisocial personality, and severe cognitive dysfunction). We identified persons with lifetime and recent (i.e., in the previous 6 months) psychiatric disorders.

Our measure of chronic medical conditions is a 15-item battery that elicits data on whether the respondent has each of eight medical conditions and whether the respondent is under medical care for the condition at the time of the interview. The conditions are chronic lung disease (emphysema, asthma, other chronic lung disease), diabetes mellitus, heart disease, hypertension, arthritis, physical handicap (amputation, paralysis, birth defect, deafness, blindness), cancer, and stroke and other neurological conditions. We developed two nested definitions of an active chronic medical condition: 1) being under care for a chronic medical condition and 2) (the more inclusive definition) either having the condition, regardless of whether under care, or being under current treatment.

The interview also elicits data on age, job status (scored by the Nam-Powers job status scale) (29), sex, marital status, and ethnicity (Mexican-American or non-Hispanic white).

We used cross-tabulations to estimate the prevalence of recent and lifetime psychiatric disorders among persons with any and each of the eight chronic medical conditions compared to persons with none of these conditions. Estimates were sex- and age-adjusted by a direct method (30). We used the 0.05 level of significance for testing the overall relationship of any psychiatric disorder to any chronic medical condition. To adjust for multiple statistical comparisons, we used the 0.01 level of significance for testing the association of each of the three major groups of psychiatric disorders (both lifetime and recent) with any chronic medical condition. The 0.005 level of significance was used to test the relationship of each of the eight specific chronic conditions to any lifetime and recent psychiatric disorder and the 0.001 level to test the association of specific psychiatric disorders with specific chronic conditions, limiting these tests to medical conditions that had any significant association with any psychiatric disorder.

To estimate the relationship between psychiatric disorder and medical conditions free of the effects of potentially confounding factors, we developed logistic regressions; lifetime and recent psychiatric disorders were the dependent variables, and the demographic variables, any chronic medical condition, and an interaction between ethnicity and any chronic medical condition were the independent variables. The interactions were not significant and were dropped from the final analyses. We developed separate analyses for each definition of a chronic medical condition and used the 0.05 level of significance to test the coefficients for any chronic medical condition.

Data were weighted to adjust for differential probability of selection within households and across the two catchment areas. The prevalences (percentages) reported here are weighted, but the sample sizes are the actual sample sizes (referred to as "actual N"). For cross-tabulations, significance tests and standard errors were corrected for the staged sampling design (i.e., they approximate exact variance estimates) using Taylor series linearization (30, 31). For logistic regressions, we estimated correction factors from a linear model (32) and applied these to the chi-square statistics for the significance of each logistic regression coefficient.

RESULTS

The sample consisted of 2,554 participants, of whom 51.5% (actual N=1,244) were Mexican-Americans. The percentage of female respondents was 50.4% (actual N=1,332); 55.5% (actual N=1,240) of the respondents were married, and 63.6% (actual N=1,617) were employed. The *unweighted* mean±SD age was 41.1±17.1 years.

The six-month prevalence of any psychiatric disorder was 19.7%, and the lifetime prevalence was 33.6% (table 1). The most common anxiety disorders were phobias; the most common affective disorders were major depression and dysthymia. About two-thirds of the substance abusers had a diagnosis of alcoholism. Almost 34% (actual N=912) of the respondents had chronic medical conditions, the most common of which were arthritis and hypertension (table 2). Across the recent conditions, 61% (actual N=595) were currently in treatment, but the percentage varied greatly by condition.

As shown in table 3, compared to respondents with none of the eight chronic medical conditions, those

TABLE 1. Recent (in Preceding 6 Months) and Lifetime Prevalence of Psychiatric Disorders Among 2,554 Persons From a Sample of the General Population[a]

Psychiatric Disorder	Recent		Lifetime	
	%	SE	%	SE
Any	19.7	0.9	33.6	1.1
Anxiety	7.7	0.6	14.0	0.8
Phobia	6.8	0.5	12.1	0.7
Panic	1.0	0.2	1.5	0.3
Obsessive-compulsive	0.8	0.2	2.4	0.3
Affective	6.8	0.6	9.7	0.7
Mania	0.2	0.1	0.6	0.2
Major depression	3.4	0.4	7.0	0.6
Dysthymia	4.5	0.5	4.5	0.5
Substance abuse/dependence	7.2	0.7	21.1	0.9
Alcohol	5.4	0.6	16.9	0.8
Drug	2.8	0.4	8.9	0.6

[a]Sample sizes vary slightly by disorder due to missing data.

TABLE 2. Prevalence of Chronic Medical Conditions and Current Treatment Among 2,554 Persons From a Sample of the General Population[a]

Medical Condition	Chronic Medical Condition		Current Treatment for Condition	
	%	SE	%	SE
Any	33.9	1.1	21.4	0.9
Chronic lung disease	4.8	0.4	2.7	0.3
Diabetes	4.2	0.4	3.5	0.4
Heart disease	4.9	0.5	3.7	0.4
Hypertension	10.4	0.6	8.8	0.5
Arthritis	14.8	0.7	5.7	0.4
Physical handicap	5.5	0.5	1.7	2.4
Cancer	1.3	0.3	1.3	0.3
Neurological disorder	1.3	0.2	1.1	0.2

[a]Sample sizes vary slightly by condition due to missing data.

with any of the conditions had about a 41% higher adjusted prevalence of recent psychiatric disorder ($t=3.09$, $df=2,550$, $p<0.001$) and a 28% higher prevalence of lifetime psychiatric disorder ($t=3.25$, $df=2,550$, $p<0.001$). We obtained a similar result when we used the more conservative definition of chronic medical conditions (current treatment) ($t=2.55$, $df=2,550$, $p<0.01$, and $t=2.17$, $df=2,550$, $p<0.05$, respectively).

When we used the broader definition of a chronic medical condition, persons with any of the conditions had a significantly higher adjusted lifetime prevalence of affective, anxiety, and substance use disorders ($t=2.65$, $df=2,550$, $p<0.01$; $t=3.00$, $df=2,550$, $p<0.01$; $t=2.70$, $df=2,550$, $p<0.01$, respectively). There were similar trends for recent psychiatric disorder. The results were statistically significant for recent anxiety disorder after adjustment for multiple comparisons ($t=3.64$, $df=2,550$, $p<0.005$). By a one-tailed test, the result for recent affective disorder was $t=2.25$, $df=2,550$, $p<0.05$ (table 3).

TABLE 3. Sex- and Age-Adjusted Prevalence of Psychiatric Disorders Among 2,552 Persons[a] With and Without Chronic Medical Conditions According to Two Definitions

Psychiatric Disorder	Condition or Current Treatment				Current Treatment			
	None (N=1,711)		Any (N=841)		None (N=2,042)		Any (N=510)	
	%	SE	%	SE	%	SE	%	SE
Lifetime								
Any	33.0	1.5	42.2[b]	2.4	34.2	1.3	41.5[c]	3.1
Affective	8.4	0.8	12.9[d]	1.5	8.8	0.7	14.7	2.5
Substance abuse/dependence	19.6	1.1	26.2[b]	1.9	20.8	1.0	21.6	2.5
Anxiety	12.4	1.0	18.2[d]	1.9	12.9	0.9	21.3[b]	2.7
Recent[e]								
Any	17.5	1.0	24.7[b]	2.1	18.3	1.0	26.6[d]	3.1
Affective	5.8	0.6	9.4	1.5	6.0	0.5	11.9	2.5
Substance abuse/dependence	6.8	0.8	8.5	1.2	7.1	0.7	7.5	2.1
Anxiety	6.0	0.6	11.9[b]	1.5	6.6	0.6	15.3[b]	2.4

[a]Two persons were excluded because of missing data.
[b]Significantly different ($t>2.81$, $df=2,550$, $p<0.05$) from percentage for persons with no chronic condition (same row).
[c]Significantly different ($t>1.96$, $df=2,550$, $p<0.05$) from percentage for persons with no chronic medical condition (same row).
[d]Significantly different ($t>2.57$, $df=2,550$, $p<0.01$) from percentage for persons with no chronic medical condition (same row).
[e]During the 6 months preceding the interview.

There were significant associations between lifetime and recent anxiety disorder and presence of a *treated* chronic medical condition ($t=2.95$, $df=2,550$, $p<0.005$, and $t=3.52$, $df=2,550$, $p<0.005$). The comparable statistics for lifetime and recent affective disorder were $t=2.27$, $df=2,550$, $p<0.05$, and $t=2.31$, $df=2,550$, $p<0.05$. There were no appreciable or significant associations of any treated chronic medical condition with substance use disorder (table 3).

As shown in table 4, when we used the broader definition of a chronic medical condition, persons with arthritis, cancer, chronic lung disease, and neurological disorder had a significantly higher prevalence of lifetime and/or recent psychiatric disorder than persons with none of the conditions (lowest $t=2.91$, $df=1,938$, $p<0.005$). By one-tailed test, persons with heart disease also had a significantly higher prevalence of recent psychiatric disorder ($t=2.63$, $df=1,849$, $p<0.005$). Persons under treatment for arthritis, cancer, and physical handicap had a higher prevalence of any lifetime and any recent psychiatric disorder than persons not under treatment (lowest $t=2.81$, $df=2,076$, $p<0.005$). In addition, persons under care for lung disease had a higher prevalence of any lifetime psychiatric disorder ($t=3.85$, $df=2,113$, $p<0.001$), and persons under care for heart disease had a higher prevalence of recent psychiatric disorder ($t=2.96$, $df=2,151$, $p<0.005$) than those not under care for a chronic medical condition.

TABLE 4. Sex- and Age-Adjusted Prevalence of Psychiatric Disorders Among 2,552 Persons[a] With Specific Chronic Medical Conditions According to Two Definitions

	Chronic Medical Condition									
	Condition or Current Treatment					Current Treatment				
		With Psychiatric Disorder					With Psychiatric Disorder			
		Lifetime		Recent[b]			Lifetime		Recent[b]	
Medical Condition	N	%	SE	%	SE	N	%	SE	%	SE
None	1,711	33.0	1.5	17.5	1.0	2,042	34.2	1.3	18.3	1.0
Arthritis	417	50.1[c]	3.7	25.3	3.5	173	63.8[c]	4.4	42.5[d]	7.6
Cancer	38	60.0[c]	6.3	30.3[c]	2.3	36	59.2[c]	7.0	30.3[c]	2.3
Diabetes	114	34.0	7.1	22.7	6.7	93	38.5	7.4	28.2	7.6
Heart disease	140	49.7	6.8	34.6	6.4	112	50.5	9.4	46.1[d]	9.3
Hypertension	291	34.2	3.7	22.4	3.9	249	32.9	4.0	18.3	3.5
Chronic lung disease	127	54.4[c]	4.6	30.9[d]	4.5	73	57.3[c]	5.9	31.9	6.6
Neurological disorder	37	46.4	5.4	37.5[c]	5.8	30	43.7	6.2	31.8	6.6
Physical handicap	148	40.6	4.4	25.8	4.1	49	43.8[d]	3.1	39.5[c]	3.2

[a]Two persons were excluded because of missing data.
[b]During the 6 months preceding the interview.
[c]Significantly different ($t>3.30$, $df\geq1,748$, $p<0.001$) from percentage for persons with no chronic medical condition (same column).
[d]Significantly different ($t>2.81$, $df\geq1,748$, $p<0.005$) from percentage for persons with no chronic medical condition (same column).

Of the six conditions that had at least one significant association with any psychiatric disorder (see table 4), four conditions (cancer, heart disease, neurological disorder, and physical handicap) had at least one significant association with lifetime and/or recent anxiety disorder after correction for multiple comparisons (lowest $t=3.29$, $df=2,070$, p about 0.001). The other two conditions (chronic lung disease and arthritis) were significantly associated with lifetime substance use disorder (lowest $t=4.00$, $df=1,836$, $p<0.001$).

The presence of a chronic medical condition was significantly associated with lifetime and recent psychiatric disorder, even after we controlled for demographic factors (i.e., age, sex, ethnicity, education, marital status, job status). The logistic regression coefficient for chronic medical condition in predicting lifetime psychiatric disorder was 0.20 (adjusted $\chi^2=9.87$, $df=1$, $p<0.01$) for the broad definition and 0.17 (adjusted $\chi^2=6.73$, $df=1$, $p<0.01$) for the narrow definition. The coefficients for predicting current psychiatric disorder were 0.22 ($\chi^2=11.40$, $df=1$, $p<0.001$) and 0.26 ($\chi^2=11.70$, $df=1$, $p<0.001$), respectively.

DISCUSSION

In this paper we provide the first estimates of the association of psychiatric disorder and chronic medical conditions in a general population. Our results are consistent with the hypothesis that there is a strong association between the two types of health problems: there was a 41% increase in the relative risk of having any recent psychiatric disorder as a function of having a chronic medical disease. Our results also support the hypothesis that affective, anxiety, and substance use disorders are each more prevalent in persons with chronic medical conditions. More than 11% of the persons with chronic medical conditions had a recent anxiety disorder. These results suggest that providers of health care should be encouraged to recognize and treat anxiety disorders in patients with chronic disease. The recent literature on coexisting psychiatric and medical disease has focused more on affective disorder than anxiety disorder. Our finding of a high prevalence of both recent and lifetime affective disorders among persons with chronic medical conditions is consistent with reports of a large number of earlier studies based on outpatient populations (5, 8, 12, 13).

Substance use disorder was the most prevalent lifetime psychiatric disorder, and chronic medical conditions were associated with a greater prevalence of lifetime substance use disorders. The importance of this finding is enhanced by current concerns that clinicians often fail to detect substance abuse and that clinical training programs underemphasize assessment and treatment of these disorders. The lack of a significant association with recent substance use was partly due to the poorer precision of the test for that association.

Certain chronic medical conditions—arthritis, cancer, chronic lung disease, neurological disorder, and heart disease—emerged as especially strongly associated with psychiatric disorder. The literature includes evidence supporting each of these associations on the basis of treated samples (5, 8, 10, 12). Contrary to other reports in the literature (13, 19, 20), we found no significant associations between psychiatric disorder and hypertension, the most common chronic medical illness. A sample of the general population would be expected to include many persons with mild hypertension, and this group might have a low prevalence of psychiatric disorders secondary to hypertension. However, even for hypertensive patients under treatment, who should have more severe hypertension, we found no appreciable or significant association with psychiatric disorder. The discrepancy between our result and that of previous studies may reflect differences in the

definition of psychiatric disorder, the severity of illness (e.g., presence of end-stage disease), or the characteristics of the contrast (no disease) group.

Previous studies have drawn mixed conclusions about the association of depression and diabetes (6). We found no significant associations between current diabetes and psychiatric disorder. The prevalence of recent psychiatric disorder, however, was 18.3% for those not under treatment for a chronic condition and 28.2% for those under treatment for diabetes—a moderately large but statistically nonsignificant difference. Thus, there may be an association between *treated* diabetes and psychiatric disorder that our tests did not have the precision to detect.

When we limited our definition of recent medical conditions to conditions under treatment, we observed a pattern of results generally similar to that for any recent medical condition, except that, as expected, the treated patients had a slightly higher prevalence of psychiatric disorders. This higher prevalence was striking for patients with arthritis and physical handicap, the two conditions with the lowest proportion of affected persons under care. One possible explanation for these results is that most persons in the general population who have arthritis and physical handicap have mild conditions which neither require care nor lead to secondary psychiatric disorders. However, the relatively few treated persons may have more severe conditions that cause secondary psychiatric disorders.

Unlike most previous research, the present study included a measure of specific *DSM-III* disorders. The measure of chronic medical conditions was a simple set of self-report items, similar to that used in several previous household health interviews. This measure could have been subject to response biases, for example, poor understanding by respondents of concepts such as "high sugar or diabetes."

The household population in the study included an approximately equal number of Mexican-Americans and non-Hispanic whites and thus differs from the general U.S. adult population. However, we found that strong relationships between psychiatric disorder and chronic medical conditions remained after we controlled for ethnicity and interactions between ethnicity and medical condition. The conclusions should be tested in general populations in other geographic sites and in other ethnic groups, e.g., blacks and Asians.

In sum, our results document a higher prevalence of recent and lifetime psychiatric disorders among a general population with one or more of eight chronic medical conditions than among persons without any of the conditions. Particularly noteworthy is the high prevalence of recent anxiety disorder in persons with chronic medical conditions. Our findings beg many interesting questions about the causal relationships between medical and psychiatric disorders; for example, to what extent does psychiatric disorder result from or contribute to chronic lung disease? Such questions must be addressed in a new generation of prospective studies of concurrent psychiatric and medical disorders.

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Fictional Depiction of Suicide in Television Films and Imitation Effects

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Studies of imitative suicide by viewers of fictional depictions of suicide in television films have produced contradictory findings. Using a nationwide sample of cases of suicide, the author found no evidence for increased numbers of suicides after broadcast of three films. However, some support was found for an imitation effect specific to the depiction of a suicide method in one of these films ($p<0.05$). To the extent that fictional presentations of suicide may serve as stimuli for imitative behavior, the effect appears to depend on a complex interaction among characteristics of the stimulus, the observer of that stimulus, and conditions of time and geography.

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Increasing attention has been focused on the role of exposure to another's suicide as an antecedent stimulus for imitative behavior, especially by the young (1–4; D. Shaffer and M. Gould, unpublished data). Beginning with an alleged rash of imitative youth suicides following the fate of the hero of Goethe's *The Sorrows of Young Werther*, when it was published in 1774 (5), suicides described in fiction have been held accountable for influencing copycat behavior. Empirical study of the impact of fictional presentations of suicide, however, is quite recent and focused exclusively on the role of television.

Several European studies have produced conflicting findings. Holding (6, 7) reported on the impact in Edinburgh of an 11-part weekly television series, "The Befrienders," which depicted a suicidal person helped by the Samaritans. He documented a 140% increase in referrals over the subsequent year but no change in the number of patients who were treated at or by the city's hospitals for attempted suicide. The effect of the series on suicides and deaths of undetermined causes was inconclusive, according to a 10-week comparison before and after the series (8). In contrast, a study of the effects of a six-part serial shown on West German television that dealt with a 19-year-old student who threw himself in front of a train found a significant increase in railway suicides by young males, those most closely resembling the age and sex of the model, during and after the period of broadcast (9). A recent report from Great Britain, however, documented no increase in imitative parasuicides after that of a popular evening soap opera character (10).

In the United States, Phillips (11) found increases in both suicides and equivocal suicides (single-vehicle motor vehicle fatalities) after suicides by characters in daytime serials on television. However, Kessler and Stipp (12) criticized his methodology and in reanalyses invalidated these findings.

Gould and Shaffer (13) studied four made-for-television movies dealing with suicide. Using a sample of adolescents who had committed suicide, taken from New York City and 28 surrounding counties, they reported a significant excess of suicides, compared with the number predicted, in the 2 weeks after the broadcast of three of the films. In addition, a retrospective examination of attempted suicides reported by six metropolitan New York hospitals found a significant increase in attempts by teenagers after, compared to before, the broadcast of all four films. Significant increases in adolescent admissions to a suburban Connecticut psychiatric emergency service due to suicide attempts by drug overdose were also reported after the presentation of one of the films (14, 15).

Eisenberg (16), in an editorial comment on the Gould and Shaffer study, stressed the urgency of further research because of the importance of the public health problem of teenage suicide and the "strength of the evidence of the phenomenon of imitative suicide." Indeed, if Gould and Shaffer's finding of a projected excess of 80 deaths nationwide over the expected number is replicated, there are significant implications for media presentation of suicide and for the use of media in suicide prevention education.

One replication of Gould and Shaffer's study has recently been reported. Phillips and Paight (17), using the same methodology as Gould and Shaffer, found no evidence of an increase in teenage suicide in the states

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of Pennsylvania and California after presentation of the same films. Phillips and Paight concluded that it therefore was "premature to be concerned about possibly fatal effects of fictional televised films about suicide."

It is important to note that there are several other, quite substantive, reasons to further replicate Gould and Shaffer's research. First, their statistical treatment of the data was inconsistent. The overlap in timing between two films was quoted as reason to exclude one film from the analysis of subjects who had committed suicide; but, inexplicably, this film was included in their analysis of subjects who had attempted suicide. Had this film been included in the analysis of subjects who had committed suicide, or excluded from the analysis of those who had attempted suicide, no significant differences would have been found.

Second, the imitative effect documented was inconsistent. There were significant differences in postbroadcast suicides for some but not all films. Two films, broadcasts II and IV, were quite similar in the amount of collateral educational material distributed nationwide concurrent with the broadcasts; yet, there were marked differences between these two films in the number of postbroadcast suicides. After a third film, broadcast III, which depicted the adolescent star behaving in a proactive manner, attempting successfully to talk his father out of suicide, there was also a significant increase in the number of suicides. Gould and Shaffer aggregated the data for these films, as necessitated by the small number of cases in their study; however, they were unable to assess the specific features of the stimuli that might account for the differential impacts of the films.

Third, in comparisons of the numbers of youth suicides rather than proportions (youth/total suicides), increases in youth suicide may merely reflect increases in all suicide, thereby documenting a general imitative effect, not one, as claimed, that is *specific* to youth (as similar to the televised model). Fourth, Gould and Shaffer used two different operational measures of the "expected" number of suicides, against which they compared the observed number of suicides or attempted suicides.

Fifth, as exemplified by Phillips and Paight's findings (17), the New York City area may not be representative of the United States as a whole, and this fact may limit the generalizability of their findings. As but one example, the leading method of youth suicide in New York City is hanging; that for the United States is gunshot wound. Sixth, there is a question regarding the proper period of study to document the impact of media stimuli (7, 14, or 28 days) or possible incubation effects (several months). Finally, without direct evidence that those youth who did commit suicide after a television broadcast actually viewed the broadcast, a correlative research design can only lead to inferential causation.

METHOD

Because the 2-week period preceding one (broadcast II) of the made-for-television movies studied by Gould and Shaffer overlapped the 2-week period after another (broadcast I), each of these films was excluded from analysis. The two remaining films (broadcasts III and IV) used in their research were reexamined. The first film was "A Reason to Live," an NBC movie broadcast on Jan. 7, 1985, depicting a teenage boy's efforts to stop his father's threatened suicide by gun. Gould and Shaffer reported four suicides after this broadcast, compared to none in the 2 weeks before its airing. The second film was "Surviving," an ABC movie broadcast on Feb. 10, 1985, dealing with the suicides of a teenage boy and girl by carbon monoxide poisoning. In Gould and Shaffer's sample there was an increase from one to four suicides. In addition, a third film—not included in Gould and Shaffer's research—was studied. "A Desperate Exit," broadcast by ABC as an after-school special on Sept. 17, 1986, dealt with the effects of a teenage boy's suicide. No description or depiction of his method was given. This film was of particular interest because it was aired less than 1 week after publication of—and widespread publicity about—Gould and Shaffer's findings and at a time of day when parents typically would not be at home to view the broadcast with their teenager. (Of interest, over 87% of ABC's local affiliates carried this program in spite of the publicity about untoward effects. I surveyed those affiliates not broadcasting the film to assess whether their decision was motivated by this publicity. Of 28 stations, only one stated that its decision was based on the study published in the *New England Journal of Medicine*. All the others refused to broadcast the program because it was their practice not to take an after-school special during "Premier Week," the first week of their new fall season when ratings were made.)

Only cases of adolescents who had committed suicide were studied in this analysis. The sample consisted of all suicides occurring within 4 weeks before and after each film's date of broadcast; the suicides were certified by a nationwide sample of medical examiners' offices.

Medical examiners' offices were selected as follows. All states, excluding those represented in Gould and Shaffer's study area, with a minimum of 100 suicides by persons age 15–24 in 1980 (18) were selected for representation in this sample. A minimum of one medical examiner's office in each of the states was solicited to participate in the sample. As noted in table 1, of 21 offices asked, 19 (90%) agreed to participate. These included three offices that certified suicides statewide (North Carolina, Virginia, and Maryland), in contrast to offices serving an urban city or county. The 19 offices served an estimated one-fifth of the U.S. population (19.7%; N=46,630,000) and certified an equivalent proportion (21.4%; N=6,133) of all U.S. suicides in 1985 (N=28,620) (19). It should be noted that both

TABLE 1. Medical Examiners' Offices Invited to Participate in Study of Imitative Suicide

State	Total Suicides in 1980 by Persons Age 15-24 Years	State's 1980 Rank	Medical Examiner's Office	Estimated Population Served (millions)	Total Suicides in 1985
California	584	1	Los Angeles	8.02	1,050
			San Diego	2.00	335
Texas	382	2	Dallas	1.70+[a]	422
New York[b]	299	3			
Pennsylvania	265	4	Philadelphia	1.80	219
Florida	258	5	Miami (Dade County)	1.80	321
			Ft. Lauderdale (Broward County)	1.30	194
Ohio	253	6	Cleveland (Cuyahoga County)	1.60	220
Illinois	240	7	Chicago (Cook County)	5.50	543
Michigan	216	8	Detroit[c]		
Virginia	193	9	Richmond[d]	5.73	710
North Carolina	129	10	Chapel Hill[d]	6.25	802
Wisconsin	128	11	Milwaukee	0.92	116
New Jersey[b]	125	12			
Georgia	121	13	Atlanta (Fulton County)	0.70	91
Washington	120	14.5	Seattle (King County)	1.50	197
Louisiana	120	14.5	New Orleans (Parish)	0.56	73
Missouri	114	16	St. Louis	1.00	98
			Kansas City (Jackson County)	0.64	99
Massachusetts	104	17	Boston[c]		
Minnesota	102	18.5	St. Paul (Ramsey, Washington Counties)	0.57	72
Maryland/ Washington, D.C.	102	18.5	Baltimore[d]	1.49	504
			Washington, D.C.	0.65	67
Total				46.63+	6,133

[a]Dallas office certifies suicides from around the state as asked.
[b]Excluded from the study.
[c]Medical examiner's office declined to participate in the study.
[d]For entire state.

populations served and numbers of suicides certified annually varied considerably across offices sampled. Four offices (Los Angeles County, Cook County, North Carolina, and Virginia) accounted for almost one-half (46%) of all suicides certified by the sample in the calendar year 1985.

RESULTS

Following the rationale presented by Gould and Shaffer (13), most analyses were conducted on a 2-week period before and after each of the television movies. In order to assess possible time lag effects, for some analyses the study period was extended to 4 weeks. Data were available from all offices sampled. However, for the 1986 film ("A Desperate Exit"), two offices (Baltimore, Md., and Washington, D.C.) were excluded because the film was not broadcast in their area. A third office (Richmond, Va.) did not have its 1986 figures available at the time of the study.

There were a total of 702 suicides in the 2 weeks before presentation of the three films and 633 suicides after their broadcast, a 10% reduction in total suicides. For youth age 24 and younger, there was a slight but nonsignificant decrease in the total number of suicides (127 before versus 112 after; Mann-Whitney $U=3$, $p=0.35$) and no change in the proportion of youth to total suicides after (0.177) versus before (0.181) these films. Similarly, there was no change in the number (46 versus 43) or proportion (0.066 versus 0.068) of suicides by those age 19 and younger. Of 54 possible changes (office×films) measured, there were 17 increases, 16 decreases, and 21 unchanged comparisons before versus after the films ($Z=0.35$, $p=0.36$, Sign test).

TABLE 2. Suicides by Young People 2 Weeks Before and After Broadcast of Two Made-for-Television Films Depicting Suicide

Film and Time	Total Suicides	Suicides by Young People: Age≤19 Years N	Age≤19 Years Proportion	Age≤24 Years N	Age≤24 Years Proportion
"A Reason to Live"					
Before	227	15	0.066	38	0.167
After	216	16	0.074	37	0.171
"A Desperate Exit"					
Before	205	10	0.049	34	0.166
After	180	10	0.056	26	0.144

Each film was separately analyzed for changes in total suicides and proportion of suicide for samples age 24 and younger and 19 and younger. Table 2 presents the 2-week comparisons for two of the films, "A Reason to Live" and "A Desperate Exit." For neither of the films was there a significant shift in total suicides or in the number or proportion of youth suicides. What appeared to be a dramatic (24%) decrease in the number of suicides by youth 24 years old and younger after

TABLE 3. All Suicides and Suicides by Carbon Monoxide Poisoning Among Young People 2 and 4 Weeks Before and After Broadcast of "Surviving"

Comparison Period	Total Suicides	Suicides by Young People							
		Total				Carbon Monoxide			
		Age≤19 Years		Age≤24 Years		Age≤19 Years		Age≤24 Years	
		N	Proportion	N	Proportion	N	Proportion	N	Proportion
2 weeks									
Before	270	21	0.078	55	0.204	1	0.048	2	0.036
After	237	17	0.072	49	0.207	3	0.176	6	0.122
4 weeks									
Before	489	36	0.074	90	0.184	2	0.056	4	0.044
After	495	33	0.067	104	0.210	5	0.152	12	0.155[a]

[a]Z=2.77, p<0.05.

broadcast of "A Desperate Exit" was not significant when tested as a proportion of total suicides (Z=0.55, binomial test).

The only film to depict a method used by the film's lead actors to commit suicide (carbon monoxide poisoning) was "Surviving." As can be seen in table 3, while no significant changes in the number (total and for youth) or proportion (for youth) of suicides were documented, an extended time sample (4 weeks) resulted in a significant increase in suicides by youth 24 years and younger by carbon monoxide poisoning (Z=2.77, p<0.05; binomial test). A similar ad hoc test of "A Reason to Live," which depicted the male adult lead threatening to shoot himself, showed a nonsignificant 15% increase in suicides by gunshot by those 24 and younger over a 4-week study period, during which there was no increase in either youth or total suicides.

DISCUSSION

In contrast to Gould and Shaffer's study (13) and in support of Phillips and Paight's replication (17), the present study found no support for the hypothesis that suicidal behavior by fictional television characters leads to an increase in suicides by youthful viewers. There is, however, evidence to suggest an imitative effect more specific than that previously documented, i.e., that of increased use of the specific method modeled on television. This finding corresponds to that reported by Schmidtke and Hafner (9) in their West German study of railway suicides and a recent report by Berman (20), which documented a significant increase in suicides by gunshot in Los Angeles County in the 7 days after comedian Freddie Prinze's 1977 suicide by gunshot.

Evidence from this study also highlights the highly variable nature of an observed effect, making it difficult to predict the differential impact of any fictional presentation of suicide. Most significant is a geographic variation. Evidence of an increase in suicides in one county might not be present in another, similar county. Whereas Gould and Shaffer's findings of increased youth suicide were mirrored in 17 of 54 comparisons in this study, they were contradicted by 16 others. In fact, only one medical examiner's office (San Diego) documented the same trend (a decrease) for all three films assessed in this study. Had this study focused on just two films ("Surviving" and "A Reason to Live") and taken a 2-week sample of all suicides from the states of Virginia and North Carolina by those age 24 and younger, a significant decrease of 13 suicides would have been reported (Z=1.68, p<0.05; binomial test). This would have led to a projected decline of approximately 260 suicides nationwide among this age group.

Rather than use of a proportion of the total suicides for the year as a measure of the expected number for any study period (13), a more appropriate control (e.g., for seasonal effects) is the number of suicides during the same period in prior years (21). When this control period (same month, same days of prior year) was used to evaluate the impact of "A Desperate Exit," a significant temporal variation was noted. The decrease in youth suicides by subjects age 24 and younger after this 1986 film (22 suicides after versus 29 before) was matched to an unexplained but substantial increase in youth suicides during the same period the prior year (33 after versus 20 before) (χ^2=3.82, df=1, p=0.06).

It appears that to the extent there is an imitative effect of fictional presentations of suicide, the effect is interactive. Characteristics of the person, the stimulus, and conditions of the environment, among others, interact to produce the observed effect; and a more microsociological level of analysis is necessary to better understand this phenomenon (22). At this level the significant questions are as follows: 1) Is there evidence that a person who subsequently committed suicide watched the film? 2) is there evidence that the film influenced the person to commit suicide? (3) what characteristics describe those most predisposed to imitate a suicide stimulus? (4) what characteristics of the film stimulus make it more (or less) likely to stimulate an imitative suicide? (5) what are the true magnitude and duration of any observed effect? (6) is there evidence for any beneficial outcome of the presentation of films depicting suicide? and 7) are those suicides which follow a film presentation likely

to have occurred at some later date due to some other precipitant?

Illustrative of many of these questions is the following case, derived from an ongoing psychological autopsy study of these postfilm suicides:

> This 17-year-old boy died by carbon monoxide poisoning in his garage soon after the Feb. 10, 1985, broadcast of "Surviving," which depicted the suicides of two teenagers by carbon monoxide poisoning. He left a diary in which he wrote extensively during the last 2 years of his life. The diary documented considerable suicide ideation during this period, as well as a prior suicide gesture and one other failed attempt to commit suicide by carbon monoxide poisoning well before the television broadcast. Significant rage toward his absent father and conflict with his mother after their divorce was expressed. Most importantly, he wrote of his confusion and pain related to questions of his sexual identity. Of "Surviving" he wrote, "I loved that film." However, of another television movie, "Consenting Adults," which aired shortly before "Surviving" and dealt with the topic of homosexuality within a context of lack of family support, he wrote, "the movie reminded myself of me 100% . . . . I feel exactly about males as he did. I feel like I'm lying to myself."

For this adolescent the choice of carbon monoxide poisoning as a method of suicide was selected and rehearsed well before its depiction in the film "Surviving." In addition, it appears that his predisposition to suicide certainly was established over some time and that feelings of heightened conflict and distress regarding his sexuality were activated by a second film he viewed before watching "Surviving." It is possible that "Surviving" stimulated or reactivated a preconceived model and method of conflict resolution, one that he used this time with fatal consequences. We are left to ponder whether his suicide would have occurred had he not seen the first film in combination with the second and/or whether any of a number of other stimuli, at some future time, would have precipitated this fatality.

An individual strongly predisposed to suicide who has yet to act on the suicidal urge may well be described as ambivalent. Ambivalence is considered by suicidologists to be common to the suicidal attitude (23). This often precarious balance between a chosen life and a chosen death may tip in the direction of either life or death in response to any of a variety of stimuli. It is possible to argue that film presentations of suicide could shift this balance toward life. An example of such a beneficial effect might be an increased sensitization of viewers to the problem of adolescent suicide, resulting in an increase in referrals (both self and others) for treatment after presentation of these programs.

With regard to negative effects, there does not appear to be significant evidence that new suicides are created by these stimuli. Rather, on the basis of the present findings, it appears most conservative to conclude that film presentations of suicide may present or model a method of suicide which, if viewed by an observer already predisposed to suicide, may be seized upon as the final solution. To the extent that the presentation of fictional suicidal acts on television provides a stimulus and model to a youth predisposed to suicide, it appears advisable to minimize the depiction of specific suicide methods. However, the more significant research focus must be on better understanding the interaction between these stimuli and those individuals predisposed to be influenced by them.

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The *Journal*'s New Program of Statistical Review

The increasing sophistication of psychiatric research over the past decade or two is, not surprisingly, reflected in the growing use of statistical methods in the scientific reporting of the findings of such research. A survey of the articles published in the *Journal* during the first 6 months of 1978 and of 1987 shows an increase from 36% to 72% in the number of scientific papers employing univariate and multivariate statistical analyses. This, in turn, is merely a reflection of the growing number of statistically based manuscripts submitted for editorial consideration.

Any satisfaction, however, in the increased scientific cast of the *Journal*'s contents must be tempered by an awareness that statistical analyses are often faulty. White, for instance, demonstrated that nearly half of the papers published in one psychiatric journal during a single year contained statistical errors, some serious enough to invalidate the authors' findings and conclusions (1). The problems that the reporting of such misinformation can cause for clinicians and investigators alike are self-evident. Equally damaging is the fact that the content of professional articles is often reported in the mass media; this, at worst, can lead to the dissemination of erroneous data and theories among the population at large. And finally, when treatment programs and public health policies are created on the basis of poorly designed scientific studies, patients may suffer. The guidance of the statistically knowledgeable is, therefore, critical to enhance the validity of statistically based papers published in the *Journal*, especially since many readers may be unable to judge for themselves the appropriateness and quality of the statistical designs and methods employed.

Although in the past the *Journal* has had the benefit of ad hoc statistical consultation for selected papers, in the light of the considerations noted above we have recently adopted a more systematic statistical assessment of manuscripts whose findings and conclusions rely on statistical methods. All statistical papers that by more general editorial criteria appear potentially worthy of publication are initially screened by our Statistical Editors, and, if more extensive statistical assessment is indicated, are sent for further review by a member of the special panel of statisticians who have kindly agreed to participate in the review process.

The general guidelines for reporting statistics are set forth in the "Information for Contributors" published regularly in the *Journal*, but it may be useful to our readers to outline some of the key points we look for while undertaking a statistical review. What are our statistical referees asked to assess in the manuscripts referred to them for review?

While such reviews are meant to focus primarily on the appropriate use of statistics themselves, they are expected to provide an evaluation of broader methodological aspects as well. For example, our reviewers address such research design issues as appropriate randomization of control groups, the relevance of comparison groups, and bias in sample selection and attrition and, more generally, they will seek to determine whether the methodology and its attendant statistical analysis are germane to explicitly and clearly stated investigative aims. In addition to assessing a paper's methods, we ask reviewers to consider whether its conclusions are, in fact, supported by the data and whether they are sufficiently tempered to the magnitude of the study's findings and its possible methodological limitations. We are not likely to respond enthusiastically to generalizations about human nature that are based on

a small sample which happened to be convenient. Reviewers, moreover, are urged to be on the lookout for findings that have great statistical significance in a technical sense, but are of only limited theoretical or clinical significance. In addition to these more global concerns, our reviewers look for conformity with the *Journal*'s requirements that authors include the names of statistical tests used and the degrees of freedom, note whether one- or two-tailed tests were used, report standard deviations rather than standard errors of the mean, and provide references to papers describing tests not in common use. Our statistical reviewers are able to offer useful suggestions to an author, such as the recommendation to use a more appropriate statistic (e.g., kappa for percent agreement or intraclass correlation for product moment correlation in assessing reliability of measurement), a multivariate analysis in place of a series of redundant univariate analyses, or a Bonferroni correction to correct for inflated type I error when evaluating a lengthy series of tests.

While our aim in this new program of statistical review is thus to ensure the appropriateness and accuracy of the statistics published in the *Journal*, we must reassure our readers and authors that we are not intent on methodological purity for its own sake. Our objective is to strengthen the scientific quality of the statistically based research that appears in the *Journal*'s pages. Many of our statistical reviewers are experienced clinicians who have also developed extensive knowledge of research methods and their application to the study and treatment of psychiatric patients, and they are fully aware of the interests and needs of authors and readers alike. We have no intention of allowing the statistical tail to wag the *Journal* dog.

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Preschool Children's Erroneous Allegations of Sexual Molestation

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Occasionally, a preschool child may erroneously accuse a parent of molestation. When this occurs, the child usually believes that his or her story is correct. A false accusation can be made when an adult has persuaded a child that the sexual events actually occurred, when a child in the oedipal stage has misinterpreted caregiving ministrations, when a child's thought processes are confused by primary process material, or when a child is secondarily involved in the projective identifications of a dominant caregiver. More than one of these mechanisms may operate in a given case.
(Am J Psychiatry 1988; 145:989–992)

Until recently, the sine qua non of sexual abuse investigations has been that "children don't lie" about molestation (1). Indeed, there is good reason to believe children when they report sexual abuse, since abused children must overcome fear, guilt, and embarrassment when they purposefully make such disclosures (2). Even though abuse is a relatively common occurrence, abused children often have not been believed (3). Misdiagnoses and failures to protect children are unfortunate byproducts of the denial that child abuse exists (4).

Allegations of sexual abuse are especially likely to occur in the course of custody disputes. Guyer and Ash, in a review of 400 court-ordered custody evaluations (paper presented at the annual meeting of the American Academy of Psychiatry and the Law, Los Angeles, Oct. 17, 1986), found that 33% of these cases involved allegations of sexual abuse. Some of the allegations were false, and many more could not be substantiated. Benedek and Schetky (5) were unable to document charges of sexual abuse in 10 of 18 custody cases, and Green (6) found that four allegations out of a total of 11 were false in a similar sample. Other cases of false allegations have been described by Brant and Sink (paper presented at the annual meeting of the American Academy of Child Psychiatry, Toronto, Oct. 12, 1984) and Schuman (7).

Most of the allegations of molestation that are made in the course of custody disputes are declarations by one parent about the other, without the direct involvement of the child. One parent "knows" that the other would do something like that. Most of these parents do not actively enlist their children in their petitions. These allegations are less likely to be correct than when a child initiates the accusation. In the course of a custody dispute, when a child spontaneously accuses a parent of molestation, the allegation is far more likely to be correct (A. Yates and T. Musty, paper presented at the 140th annual meeting of the American Psychiatric Association, Chicago, May 9-14, 1987).

The mechanism by which preschool children come to make false accusations may differ from the mechanisms involved in accusations by older children and adolescents. Kaplan and Kaplan (8) presented the case of a 5-year-old girl who, during a custody and visitation dispute, accused her father and paternal grandfather of molestation. The girl seemed locked in a *folie à deux* relationship with her mother, who was eager to believe and report the accusations. Green (6) reported two additional cases in which apparently false allegations were made by preschool children. The first was of a 3-year-old boy who appeared to accept his mother's paranoid delusions in his accusations of incest against his father. The second was that of a 4-year-old boy who revealed, after some months of therapy, that his reluctant testimony (in the presence of his mother) against his father was not true. He had lied because of

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pressure from his mother. In our literature review, this was the only case of a preschool child who was consciously aware of the deception, although Terr (9) described an 8-year-old who seemed, in retrospect, to have knowingly tricked the authorities when she was 3 years old.

Schetky and Green (10) suggested that children who make false accusations tend to speak easily and with an absence of negative affect about the sexual events they describe, unlike children who are correct in their accusations. Children who make false accusations may parrot phrases, use adult sexual terms, or be sexually preoccupied, but they do not exhibit other symptoms, and they often relate warmly to the accused parent.

Some mechanisms by which young children may come to make erroneous allegations that they perceive to be true are 1) through the persuasion and/or suggestion of a caregiver, 2) through sexualized perceptions emanating from the oedipal conflict, 3) through the emergence of primary process material, and 4) through the secondary involvement of the child in the projective identifications of a dominant caregiver.

The following cases involve preschool children who made direct allegations of molestation that were false or that could not be substantiated. These cases were private referrals and represent a highly selected sample, presented to illustrate some of the characteristic dynamics.

CASE REPORTS

Case 1 (persuasion). During a custody dispute, Ann, a 4-year-old girl, described how her father had rubbed her "tushy" and how it had felt good. On the stand she was unable to provide further details. In response to the defense attorney's questions, she stated that she had not been able to remember the events herself but that her mother had reminded her again and again. Later, the mother testified that she thought that the events had probably happened.

Young children are susceptible to persuasion, "brainwashing," or bribery because they are dependent and gullible and usually want to please important adults. They have a limited fund of information and experience with which to critically evaluate what is said, and they can easily maintain opposing views of people or events. However, children who are misled are often inconsistent in recalling the events. Their affect may not be appropriate, and they are unable to provide details about time, place, and so forth.

Case 2 (oedipal influences). When Beth was 3 years old, her parents were divorced and her father moved to a nearby city. Beth visited her father for 1 week every other month and for 2 months during the summer. She had always been close to him and the visits went smoothly. During vacations, Beth's father would take her with him when he went hiking and camping in the mountains. They sometimes slept in the same sleeping bag for warmth or because Beth was afraid of wild animals.

When Beth was 5 years old, her father introduced her to his new fiancée. On arriving home after the visit, Beth seemed sullen and angry. Her mother questioned her about abuse, and Beth agreed that she had hugged, touched, wrestled, been in bed with, and been naked with her father. She nodded when asked, "Does he try to make love to you?" She appeared sad and tearful during the questioning.

After a preliminary evaluation by Child Protective Services, visitation was suspended and Beth was assigned to a weekly play therapy group for sexually abused children. She attended 25 sessions, during which she was urged to recount or play out abusive experiences with the anatomically correct dolls. The fact that Beth did not reveal any sexual experiences on her own was interpreted by the therapist as resistance and an indication that she needed more therapy. Eventually, Beth, her mother, and her father were evaluated by a child psychiatrist who noted that the father seemed to have been involved in caregiving activities which were expectable for a single parent and that Beth understood "making love" as "liking an awful lot." The case was dismissed.

In retrospect, Beth's affirmative responses to the questions about molestation seemed to be related to her oedipal "romance" with her father, the nature and content of the questions asked, and the fact that she and her father did have a physically close, affectionate relationship. The referral of a child after a preliminary (and inconclusive) evaluation to a play group for sexually abused youngsters is highly questionable, as there may be subtle pressures on the child to act as if she or he has been abused so as to be accepted by the others in the group. This in turn could prejudice subsequent evaluations. Until there is definitive research in this area, common sense dictates that a child not be included in a group for sexually abused children until the existence of abuse has been confirmed. Instead, the child can be assigned to a regular therapy group, where any unusual, sexualized behavior can be documented.

Oedipal fantasies are especially persuasive and may be the basis for an erroneous accusation of molestation (11). The vigorous investigation methods that are currently used may elicit oedipally based fantasies, because the child is asked direct, explicit questions that are not asked in other situations. Although an oedipally involved child may play out bedroom, bathroom, or spa scenes with the anatomically correct dolls, the child is unlikely to depict the specifics of penile insertion or oral intercourse, which a sexually abused youngster might do.

Case 3 (psychiatric disorders). Carl's parents had separated when he was 3 years of age. In spite of generous visitation arrangements, the father continued to accuse the mother of multiple inadequacies as a parent. The battle in court continued even after the father had remarried and fathered another child.

Carl was 5 years of age when he first reported that his mother had hit him with her fist, kicked him, and pinched and bitten his private parts. He told a Child Protective Services worker that she "bit my penis so hard that I peed in her mouth." Carl was described as an angry, aggressive, sexualized child who was impulsive and excitable. His full-scale IQ was 128. Responses to the Thematic Apperception Test in-

cluded, "The mom and the little boy are riding [on the bicycle], and the baby crawled out of her shirt and kicked her boobs by accident. She stopped, and the boy had a bike, and his front wheel went up her dress, and his back wheel skidded and knocked her down." Another response was, "The two little babies were in the crib, and they farted and peed in their pj's, and their mom spanked their butts so hard they fell off." In shelter care Carl engaged in genital exhibitionism, lying, and manipulation. He attempted sex play with other foster children, was fascinated with the dog's genitals, and enjoyed talking about molestation. He accused his therapist of molesting him when the therapist helped him out from under a table, and he claimed that his shelter care father walked around with his pants down.

The mother was described as skillful in her parenting techniques but confused and upset by the father's accusations. The father was a physician who became easily angered when things did not go his way. He would go to extraordinary lengths to force another person to conform to his expectations. Both parents provided Carl, the only child of that marriage, with copious attention.

Although all but one of the many examining psychiatrists and psychologists doubted that any sexual abuse had occurred, the court ordered that the child remain in his father's home, with sharply limited visitation by the mother to protect her from further charges of molestation. All charges of molestation were dropped, but the custody dispute continued.

Carl closely identified with his intense, opinionated father, whom he perceived as omnipotent. He needed to fuse with the powerful aspects of his father as an important defense against his underlying sense of helplessness. Although the father persistently denied trying to influence the child, his anger at the mother was evident. Carl appeared to be sharing his father's opinion and to be acting out his father's anger at and dislike of his mother. Carl's chaotic thinking, imbued with primary process material, and his impaired reality testing were important contributing factors.

Case 4 (shared perceptions). The mechanism by which a healthy child may come to share a parent's frame of reference is illustrated by the case of Donna, a 2-year-old girl who lived with her mother. At the time of the parents' stormy separation, the mother had reported a suspicion of sexual abuse to Child Protective Services. Subsequent medical and Child Protective Services evaluations did not substantiate these claims. In spite of this, after each of Donna's visits with her father, the mother would inspect Donna's genital area thoroughly, and she often questioned her about sexual abuse. Later, the mother took Donna to a mental health clinic for an abuse evaluation because the child seemed afraid of men. On the basis of the play evaluation, the child was described as afraid of being physically and sexually hurt. The mother was described as having unresolved problems in sexual relationships and relationships in general with men. Donna's therapist did not see any sexual themes in her play until 4 months had passed, when she put a male doll in the vaginal area of a female doll and said to the therapist, "Biting, biting, biting." She could not elaborate, and a medical examination revealed no evidence of sexual abuse. Subsequent court and psychiatric evaluations did not substantiate the allegations of abuse. The father was assigned supervised visitation, not to protect the child from her father but to protect her from further vaginal inspections and involvement in her mother's fantasies.

Donna's mother presented herself as absolutely convinced that her daughter had been sexually abused. She communicated to Donna her concerns about the dangerousness of men and the likelihood of genital injury. Although Donna continued to relate pleasantly to her father, she presented enough "evidence" of abuse to cause the launching of a substantial investigation. Her anxiety about men and sexuality seemed to be a manifestation of her mother's strong projections.

Cases (8 and paper by Brant and Sink) similar to the last two presented here have been explained on the basis of a *folie à deux* between the parent and the child. The *DSM-III* definition of *folie à deux*, or shared paranoid disorder, is that one individual shares the delusions of another person who has a diagnosable paranoid psychotic disorder. In the cases of Carl and Donna, the dominant parent was strongly opinionated and perhaps emotionally disturbed, but not psychotic. A more accurate construct for these cases would be that the children were included in and shared the projective identifications of authoritative adults.

Projective identification is a common pathological mechanism not limited to psychotic patients and is especially common in individuals with a borderline personality organization (12). Horowitz (13) described projective identification as an intrapsychic and interpersonal phenomenon that is often present in intimate relationships and marital interactions. The permeability of ego boundaries that is a characteristic of intense involvement permits the transfer of a range of mental content back and forth between the individuals involved. According to this formulation, in custody cases with false accusations, one parent, the accuser, projects sexual and aggressive impulses onto the other parent in an attempt to dominate, devalue, or control. The attack is engendered by primitive envy and the unconscious wish to cling parasitically to the other person. The accused parent, who becomes the receptacle for the disturbed projections, feels unfairly put upon or manipulated in someone else's fantasies and responds with irritation or anger. This serves to confirm the truth of the allegations in the mind of the accuser, who launches further flagrant accusations in an attempt to control the accused and prevent more transgressions. In spite of the single-minded fury of the attacks, the attacker often wishes to be reunited with the accused, who is both loved and feared. In a custody dispute this oscillation of projection and introjection becomes intensely frustrating and confusing to all concerned. The accuser rejects attorneys and psychiatrists who will not agree with his or her distorted perceptions. These cases tend to drag on interminably without any clear resolution.

The child, under the influence of the dominant parent, is secondarily involved in the parent's distortions. The sharing of projective identification is facilitated by

the child's dependent position, lack of a crystallized identity, and limited information base. The parent's projective identification can continue to influence the child when the parent is temporarily absent, so the child may provide a clear and persuasive indication of abuse during an evaluation (7).

DISCUSSION

The children we have described were "telling the truth." Preschool children who progress through the child sexual abuse legal system to the point of psychiatric evaluation usually do believe that "bad," "dirty," or sexual events occurred. In our experience, young children rarely or never sustain fabrications about sexual molestation, even when they clearly wish to be placed with one custodial parent. However, there have been sporadic case reports in which a preschool child did seem to be consciously fabricating a tale of molestation (6, 9), and this problem certainly warrants further exploration.

The question arises as to whether children should be confronted—and how and by whom—to determine if their accusations are false. When children who have been persuaded by a caregiver, who misinterpret events because of the oedipal conflict, or who suffer from a thought disorder are confronted, they are unlikely to change their "true" stories. However, children who share the projective identification of a caregiver often change their attitudes and their stories when they are removed for a period of time from the accusing parent and are placed in the presence of the parent they have accused. Such a change is related to the diminished influence of the absent parent's projective identification and the reality of the other parent's presence.

Occasionally, during a custody dispute, a youn child may accuse an adult of sexual misconduct. Suc an allegation clearly demands thorough and objectiv evaluation. However, even an exhaustive investigatio by skilled examiners may not absolutely prove or dis prove the allegation, which can leave the disturbin possibility that the unsubstantiated allegation is co rect.

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Efficacy of Anticholinergic Prophylaxis for Neuroleptic-Induced Acute Dystonia

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The authors analyzed data from nine studies comparing the incidence of acute dystonia induced by neuroleptic agents with and without concomitant use of anticholinergic agents. Anticholinergic agents reduced the rate of dystonia by 1.9-fold in all patients treated with different neuroleptics and by 5- to 8-fold in patients treated with high-potency neuroleptics. In addition, the incidence of dystonia and the efficacy of anticholinergic prophylaxis were related inversely to age. These results support the efficacy of anticholinergic agents in preventing neuroleptic-induced dystonia, particularly in young male patients treated with high-potency neuroleptics.

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The use of anticholinergic agents to prevent neuroleptic-induced dystonia has remained controversial despite 35 years of clinical experience with neuroleptic therapy. In 1970, DiMascio and Demirgian (1) concluded that anticholinergic prophylaxis for neuroleptic-induced acute dystonia might be unnecessary, based on a review of available reports and their experience with 344 patients. In 1977 Swett et al. (2) corroborated this view, finding that anticholinergic agents were ineffective in preventing neuroleptic-induced acute dystonia in 654 patients treated with chlorpromazine. Since then, however, a growing number of reports (3–11) have suggested that the rate of neuroleptic-induced acute dystonia may be reduced with concurrent use of anticholinergic agents.

In addition, the reported incidence of neuroleptic-induced acute dystonia has increased over the past two decades. In 1961 Ayd (12) surveyed 3,775 patients treated with neuroleptics and reported a mean risk of 2.3%, but more recent studies (3–9, 13–16) have reported rates of 21%–94% in patients not treated with an anticholinergic agent. The apparent rise in dystonia rates may correspond to trends toward increased use of high-potency neuroleptics, especially in high initial doses (17, 18).

Because the efficacy of early use of antiparkinsonian agents to minimize the risk of neuroleptic-induced acute dystonia remains unclear, particularly with respect to high- versus low-potency neuroleptics, we have compiled and reanalyzed pertinent studies to try to clarify these issues.

METHOD

We reviewed the available literature on the concomitant use of neuroleptic and antiparkinsonian agents in the treatment of psychotic patients, including studies providing data concerning the incidence of acute dystonia with and without use of antiparkinsonian agents. Studies were evaluated for their design, but retrospective or open studies were not excluded if data comparing antiparkinsonian-treated and untreated cases were provided. Studies involving only high-potency antipsychotic drugs and controlled trials were assessed separately. For studies in which the original reports did not provide data separately for high-potency agents or for haloperidol (the most commonly used high-potency agent), we obtained additional breakdowns of the original data from the investigators involved (4, 7).

Data thus gathered were subjected to the Mantel-Haenszel method of chi-square analysis (19) with Yates' correction for small sample sizes and with one degree of freedom, which permits assessment of the effect of antiparkinsonian prophylaxis across all studies as well as an assessment of the variability of this effect among trials (20). Correlations were tested with Pearson's (linear regression) and Spearman's (rank

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TABLE 1. Studies of Anticholinergic Prophylaxis of Neuroleptic-Induced Acute Dystonia

Study	Year	Number of Subjects	Subjects' Mean Age (years)	Male Subjects (%)	Neuroleptic and Dose (mg/day)[a]	Antiparkinsonian and Dose (mg/day)[b]	Design
Hanlon et al. (19)	1966	122	38	0	Perphenazine, 5	Benztropine, 1.3	Random, blind
Swett et al. (2)	1977	654	35	50	Chlorpromazine, 6	Benztropine, 2	Open
Stern and Anderson (3)	1979	40	29	50	High- and medium-potency neuroleptics or mixture of different agents, 9	Benztropine, 2	Retrospective
Keepers et al. (4)	1983	215	29	52	Any (60% haloperidol, 16)	Any	Retrospective
Manos et al. (7)	1986	42	30	64	Any (45% haloperidol)[c]	Trihexyphenidyl, 5[d]	Random, blind
Stramek et al. (5)	1986	202	33	81	Any (47% haloperidol, 16)	Any, 4	Open
Winslow et al. (6)	1986	39	27	56	High-potency neuroleptics, 23	Benztropine, 4	Random, blind
Arana et al. (9)	1987	29	35	100	Haloperidol, 14	Benztropine, 4	Random, blind
Boyer et al. (8)	1987	23	24	87	Haloperidol, 20	Benztropine, 1-2	Retrospective

[a]Mean haloperidol equivalents (21).
[b]Mean benztropine equivalents (21).
[c]72% had haloperidol with or without another neuroleptic.
[d]Mean dose at 4 weeks for all patients.

correlation) methods to obtain a coefficient (r or rho, respectively).

RESULTS

Data were obtained from nine trials involving a total of 1,366 patients (table 1). No antiparkinsonian agents other than anticholinergic drugs were used in these studies, and most involved benztropine. The overall effect of prophylaxis with different types of neuroleptic agents was to reduce the risk of developing acute dystonia from 14.8% to 7.7%—a moderate but statistically significant effect of reducing the risk by 1.9 (table 2). Although there was significant variation in results among the studies, five of these nine trials individually showed significant effects and one study involving only female patients showed no dystonia in any patient (table 2).

Additional analysis of results from the six trials involving 330 patients receiving only a high-potency neuroleptic (mainly haloperidol) (4–9; reworked data by Dr. Keepers; personal communication from Dr. Manos) yielded a greater, highly significant overall difference of 51.2% versus 9.5.%, or a 5.4-fold reduction of risk of neuroleptic-induced acute dystonia, significant in four of six individual trials (table 2). Similar results were obtained for five studies involving 291 cases with haloperidol as the only neuroleptic (4, 5, 7–9; reworked data by Dr. Keepers; personal communication from Dr. Manos). There was a 5.36-fold reduction in risk from 46.8% to 8.72% ($\chi^2=34.0$, df=1, $p<10^{-6}$). This apparently greater relative benefit of prophylaxis with high-potency neuroleptics was further supported in a separate analysis of the three prospective, double-blind trials involving such antipsychotic agents, with a total of 110 cases (all given high-potency neuroleptics and either benztropine or trihexyphenidyl as the antiparkinsonian agent) (6, 7, 9; personal communication from Dr. Manos). There was a 7.5-fold reduction in risk from 44.1% to 5.88% ($\chi^2=17.3$, df=1, p=0.00003). When the controlled trial by Hanlon et al. (20) was included with the other controlled trials (6–9), the effect of prophylaxis changed very little (7.96-fold reduction of risk from 21.5% to 2.7%; $\chi^2=18.9$, df=1, p=0.00001, N=232).

When the incidence of neuroleptic-induced acute dystonia without prophylaxis was regressed on age, there was a strong and significant linear correlation (r=−0.836, df=7, p<0.02) as well as rank correlation (rho=−0.876, df=7, p<0.02), indicating a fall in risk of neuroleptic-induced acute dystonia of 2.11% per year between ages 15 and 45 years, after which neuroleptic-induced acute dystonia was rare. Also, when the six studies using high-potency neuroleptics (4–9) (table 2) were ranked according to the mean age of subjects, the two with the youngest patients (mean age=24 years, 8 months, and 27 years, 6 months) demonstrated relatively high rates of neuroleptic-induced acute dystonia without prophylaxis (94% and 47%) and a much greater apparent efficacy of benztropine prophylaxis (0% dystonia in both prophylaxis groups) than the two studies involving patients of greatest mean age (33 years, 5 months, and 35 years, 9 months; dystonia incidence without prophylaxis, 38% and 33%, and dystonia incidence with prophylaxis, 11% and 14%, respectively). The one study finding no risk of dystonia during treatment with perphenazine (20) involved older patients (mean age=38 years) and only women. The Spearman rank correlation for all nine of the studies reviewed, in terms of risk ratio versus age (tables 1 and 2) was also significant (rho=−0.850, df=7, p<0.03), and a similar strong trend

TABLE 2. Efficacy of Anticholinergic Prophylaxis of Dystonia

Study	With Prophylaxis			Without Prophylaxis			Risk Ratio[a]	χ^2 (df=1)	p
	N	Dystonia N	Dystonia %	N	Dystonia N	Dystonia %			
Studies using any neuroleptic	414	32	7.7	950	141	14.8	1.92:1.00	42.30[b]	<10 $^{-6}$
Hanlon et al. (19)	60	0	0.0	62	0	0.0	1.00:1.00	0.00	n.s.
Swett et al. (2)	86	4	4.7	568	19	3.3	0.72:1.00	0.09	n.s.
Stern and Anderson (3)	14	1	7.1	26	12	46.1	6.46:1.00	4.66	0.031
Keepers et al. (4)	80	9	11.2	135	51	37.8	3.36:1.00	16.30	0.00006
Manos et al. (7)	15	1	6.7	27	13	48.1	7.23:1.00	5.72	0.017
Sramek et al. (5)	116	15	12.9	86	18	20.9	1.62:1.00	1.76	0.18
Winslow et al. (6)	22	0	0.0	17	8	47.1	>40.00:1.00	10.30	0.0013
Arana et al. (9)	14	2	14.3	15	5	33.3	2.33:1.00	0.58	0.45
Boyer et al. (8)	7	0	0.0	16	15	0.0	>90.00:1.00	15.00	0.0001
Studies using high-potency neuroleptic	158	15	9.5	172	88	51.2	5.39:1.00	57.70[c]	<10 $^{-6}$
Keepers et al. (4)[d]	48	5	10.4	77	37	48.1	4.62:1.00	17.10	0.00004
Manos et al. (7)[e,f]	6	1	16.7	13	10	76.9	4.61:1.00	3.89	0.48
Sramek et al. (5)	61	7	11.5	34	13	38.2	3.33:1.00	7.86	0.005
Winslow et al. (6)[f]	22	0	0.0	17	8	47.1	35.00:1.00	10.30	0.0013
Arana et al. (9)[f]	14	2	14.3	15	5	33.3	2.33:1.00	0.58	0.45
Boyer et al. (8)	7	0	0.0	16	15	93.8	30.00:1.00	15.00	0.0001

[a]Ratio of incidence without prophylaxis to incidence with prophylaxis.
[b]By Mantel-Haenszel analysis. Variation among studies: $\chi^2=23.5$, df=1, $p=1.3\times10^{-6}$.
[c]By Mantel-Haenszel analysis. Variation among studies: $\chi^2=8.19$, df=1, p=0.0042.
[d]Data reworked by Dr. Keepers from original study.
[e]Based on a personal communication from Dr. Manos, July 1987.
[f]Random assignment, double-blind assessment used.

was shown for the six more comparable trials involving only high-potency neuroleptics (rho=−0.900, df=4, $p<0.05$).

DISCUSSION

These results indicate that the benefit of anticholinergic prophylaxis of neuroleptic-induced acute dystonia is significant and appears to be greater with the high-potency neuroleptics than with antipsychotic agents of all types (table 2); the reduction of risk was 5.4-fold versus 1.9-fold, respectively. Moreover, anticholinergic agents had no apparent effect when used with the low-potency agent chlorpromazine in the large retrospective study by Swett et al. (2) (tables 1 and 2). The seemingly greater prophylactic effect with high-potency neuroleptics appears to reflect the base rate of risk without prophylaxis, since the risk with an anticholinergic agent added was about 9%–10% regardless of the type of neuroleptic (table 2).

In addition, the variation among studies in the incidence of neuroleptic-induced acute dystonia with and without use of an antiparkinsonian agent (table 1) suggests that factors in addition to neuroleptic potency may influence the risk of dystonia and the efficacy of anticholinergic prophylaxis. Risk factors that have been identified previously for dystonia (in addition to use of high-potency neuroleptics) are youth and male sex (4, 9–13). Because of the large variety of unknown and uncontrolled variables among the studies reviewed, it is not possible to analyze reliably the relative contribution of factors other than anticholinergic prophylaxis. It is of interest, however, that there was a strong tendency for a higher risk of neuroleptic-induced acute dystonia among younger patients, as had been reported previously by Keepers et al. (4). Dystonia was rare in patients over age 45, and the efficacy of prophylactic treatment decreased with increasing age of patients. The one study that found no occurrence of dystonia with or without anticholinergic prophylaxis (20) involved older female patients treated with a low mean dose of perphenazine (22.5 mg/day, or about 5 mg/day haloperidol equivalents), an agent of moderate potency.

The analysis of pooled data from the nine pertinent studies thus strongly supports the probable efficacy of anticholinergic prophylaxis in the prevention of neuroleptic-induced acute dystonia in psychotic patients, at least in young patients treated with high-potency neuroleptics. Patients treated with chlorpromazine and patients over age 45 seem unlikely to benefit from anticholinergic prophylaxis.

Further work is needed to determine the optimal dose and duration of prophylactic treatment with anticholinergic or other types of antiparkinsonian agents and to assess the relative cost in terms of side effects. In addition, the use of lower doses of high-potency neuroleptics should be studied as another possible means of reducing the risk of neuroleptic-induced acute dystonia as well as other neurological side effects of neuroleptic agents (18).

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Imipramine and Social-Vocational Adjustment in Chronic Depression

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The authors compared the effects of 6 weeks of imipramine treatment with 6 weeks of placebo treatment on social and vocational impairment in chronic depression. Imipramine was associated with significantly greater pre- to posttreatment improvement of social-vocational impairments in chronic depression, suggesting that these impairments may have represented affective symptoms rather than characterologic deficits.

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We have recently reported that symptoms of chronic or dysthymic depression can be markedly reduced by a course of treatment with imipramine (1). Impairments of social functioning have been recognized as common and pervasive deficits in dysthymia, which often lead to major personal and business failure (2). Improvement in mood and associated depressive symptoms may be of limited value in such patients unless accompanied by improved social and vocational competence and performance. Theories about the nature of chronic depressive states have alternated between the characterologic or neurotic conceptualization and the theory that chronic depression is a variant of affective illness with likely biological determinants (3). Formulations of dysthymia as a character disorder are more likely to depict the impairment in social function as primary and predisposing and therefore as less likely to resolve even when depressive symptoms abate. On the other hand, if the social deficits are viewed as symptoms of a chronic affective illness, they might be expected to resolve promptly when other affective symptoms disappear. As part of a double-blind, placebo-controlled trial of imipramine for outpatients with chronic depression, we assessed social and vocational function before and after treatment to test these two contrasting hypotheses.

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METHOD

Subjects were recruited among adults requesting outpatient treatment for depression at the Payne Whitney Clinic and Maine Medical Center. Patients were included if they fulfilled *DSM-III* criteria for dysthymic disorder, had a score higher than 14 on the 24-item version of the Hamilton Rating Scale for Depression (4), and signed informed consent. Exclusion criteria were a history of psychosis, mania or hypomania, alcohol or substance abuse, severe or chronic medical illness, or a recent adequate trial of antidepressant medication. Details of the clinical and demographic characteristics of the complete patient sample as well as the drug treatment regimen have been reported elsewhere (1, 5). In brief, treatment was with imipramine, 50 mg, or an identically appearing placebo. All subjects initially received a single-blind placebo treatment for 2 weeks. Those who continued to satisfy the inclusion criteria were then randomized on the basis of random numbers into two groups: those receiving imipramine and those receiving placebo. Doses were gradually escalated over the first 2 weeks to a maximum of six pills per day and then remained constant over the next 4 weeks. Recovery was defined as a score lower than 7 on the Hamilton scale and improvement such that *DSM-III* criteria for dysthymic disorder were no longer met.

The Social Adjustment Scale—Self-Rated developed by Weissman et al. (6) from a social adjustment interview has been administered to large numbers of depressed and normal subjects as well as to patients having other psychiatric diagnoses; it has been demonstrated to distinguish depressed patients from normal subjects, to differentiate acute from recovered depressed patients, and to have good internal consistency and test-retest stability. In the present study, this scale was administered by trained research assistants before and at the completion of the double-blind treatment period. Items on this questionnaire are rated on a 5-point scale and pertain to eight areas of social and vocational function: work for pay, housework, school

TABLE 1. Social Adjustment Scale—Self-Report Scores of Patients With *DSM-III* Dysthymic Disorder Who Received Imipramine or Placebo[a] for 6 Weeks and Subjects From a Published Study

	Pretreatment Scores						Posttreatment Scores						Published Scores (6)			
	Dropouts (N=14)		Imipramine (N=13)		Placebo (N=12)		Imipramine (N=11)			Placebo (N=13)			Acute Depressed (N=172)		Community Sample (N=399)	
Subscale	Mean	SD	Mean	SD	Mean	SD	Covariance-Adjusted Mean	Mean	SD	Covariance-Adjusted Mean	Mean	SD	Mean	SD	Mean	SD
Extended family	2.1	0.6	2.3	0.6	2.0	0.8	1.7	1.8	0.3	2.0	2.2	0.3	2.2	0.7	1.3	0.1
Family unit	2.9	1.0	2.6	0.9	2.4	0.7	2.2	2.2	0.8	2.2	2.5	1.0	2.8	0.8	1.5	0.6
Parenting	1.6	0.6	1.4	0.5	2.3	0.8	—	—	—	—	—	—	2.3	0.8	1.4	0.4
Marital	3.2	0.8	2.5	0.9	3.1	0.8	1.9	1.8	0.1	2.7	3.0	0.8	2.5	0.6	1.8	0.5
Overall family	2.3	0.7	2.3	0.6	2.4	0.7	1.9	1.8	0.3	2.2	2.4	0.7	—	—	—	—
Leisure time	2.8	0.7	2.9	0.4	3.1	1.2	2.5	2.5	0.5	2.9	3.1	1.0	2.9	0.7	1.8	0.5
Work	2.7	1.2	2.6	0.9	2.2	0.8	1.6	1.8	0.9	2.7	2.5	1.1	2.5	0.8	1.4	0.5
Total	2.6	0.6	2.6	0.5	2.5	0.6	2.0[b]	2.0	0.4	2.6[b]	2.6	0.6	2.5	0.5	1.6	0.4

[a]Eleven patients in the imipramine group and 11 patients in the placebo group completed both pre- and posttreatment ratings.
[b]Significant difference between posttreatment groups ($F=13.45$, $df=1, 19$, $p<0.05$, based on ANCOVA with Bonferroni correction).

performance, social and leisure time activities, and parenting, as well as marital, family, and extended family interaction and performance. Subscale scores are derived from each of these areas and a total score is computed. As suggested by Weissman et al. (6), the work for pay, housework, and school performance scales were collapsed into a single work scale. In addition, we developed a mean family functioning score for each individual by averaging scores on the extended family, family unit, parenting, and marital scales.

On the same days as administration of the Social Adjustment Scale, patients were rated by a research psychiatrist using the 24-item version of the Hamilton depression scale and the Global Assessment Scale (GAS). The GAS was developed by Endicott et al. (7) to measure overall severity of psychiatric disturbance; anchor points include symptoms as well as social and vocational function. Differences in posttreatment Social Adjustment Scale scores across groups were analyzed by analysis of covariance (ANCOVA) corrected for pretreatment scores. The Bonferroni adjustment was used in determining statistical significance to protect against errors due to the number of comparisons. Differences in distribution of treatment outcome were analyzed by Fisher's exact test. Linear regression analysis was used to compute correlations among scores on all three scales.

RESULTS

Forty-one patients (27 women and 14 men; mean age, 39±12 years) completed the measures of social-vocational function during the single-blind placebo period. Ten did not enter the randomization because of clinical improvement (N=7), clinical worsening (N=1), or patient refusal (N=2). The remaining 31 patients satisfied criteria for and cooperated in randomization (imipramine, N=16; placebo, N=15), and 27 patients completed the double-blind treatment period. Seven of 13 (54%) imipramine and three of 14 (21%) placebo subjects were classified as recovered (Fisher's exact test, $p=0.01$). Three patients from the imipramine group dropped out of the study because of noncompliance (N=2) or adverse medication reaction (N=1). One placebo patient was dropped because of worsening depression.

The Social Adjustment Scale—Self-Report was completed by 13 imipramine and 12 placebo patients before randomization and by 11 imipramine and 13 placebo patients at the completion of the double-blind period. Eleven of the same patients in each group completed the scale at both time points. The subscale and total scores are shown in table 1; none of the pretreatment differences were significant among the three groups (dropouts, imipramine completers, and placebo completers) by ANOVA, and scores were normally distributed in all groups on all scales. Scores published by Weissman et al. (6) for large samples of patients with acute depression and normal subjects from the community are shown in table 1 for comparison purposes.

After treatment, scores on the various Social Adjustment subscales were essentially unchanged in the placebo-treated group, while most scores in the imipramine-treated group showed improvement. Differences were significant by ANCOVA corrected for pretreatment values on the scale's total score. Subscales measuring work performance and extended family, marital, and overall family functioning showed trends for more improvement in the imipramine group. When the posttreatment scores on the total scale were divided according to a median split, nine of 11 imipramine and three of 13 placebo patients were above the median score of 2.1 (Fisher's exact test, $p=0.025$). The correlations between improvement in the clinician-rated Hamilton scale and GAS scores and the Social Adjustment Scale total score from beginning to end of treatment were quite high and statistically significant ($r=0.50$, $df=22$, $p<0.02$, and $r=0.66$, $df=22$, $p<0.001$, respectively).

DISCUSSION

Results on scales measuring social and vocational functioning demonstrated greater improvement in imipramine- than in placebo-treated patients with chronic depression after 6 weeks of treatment. Improvement in Social Adjustment Scale—Self-Rated total scores was correlated with improvement in clinician-rated depressive symptoms and global severity of illness. Imipramine tended to produce positive effects across a range of family involvements and work and performance. The observed effects were consistent with results from another study of chronic depression treated with antidepressant medication (8). These results extend and enhance reports of favorable effects of medication on depressed mood and associated symptoms as scored by clinical raters in chronic depression (1). The practical implication of these findings is that improvement in social functioning can be expected to occur in chronically depressed individuals who respond to antidepressant medications. Improvement in these aspects of function are important; if antidepressant medication merely reduced depressive symptoms, social impairment might persist and lead to further personal and business failure and to a cycle of demoralization. A more theoretical implication of the rather prompt improvement in self-rated social adjustment with imipramine, at a time when mood and depressive symptoms were also improving, is that social impairments can be considered to be among the symptoms of chronic affective syndromes. Lack of social improvement would have suggested that such impairments represented characterologic or psychologically determined precursors, which might persist even with improvement in depressive symptoms.

Effects of treatment on social adjustment have also been reported in acute depression. Weissman et al. (9, 10) have found differential effects of psychotherapy and amitriptyline on interviewer-rated social adjustment in two separate studies. In the first study (9), evaluations were conducted at the end of treatment with psychotherapy, with amitriptyline, and with a combination of the two. The psychotherapy groups were found to have better adjustment at the end of 8 but not after 4 months of treatment. In the second study (10), acutely depressed patients received amitriptyline or interpersonal psychotherapy alone or in combination for 16 weeks. Long-term effects were assessed 1 year later when most patients were asymptomatic; patients who had received interpersonal psychotherapy alone or in combination with pharmacotherapy were doing significantly better on some measures of social adjustment than a group that had received amitriptyline alone. The authors concluded that psychotherapy had a greater effect than medication on social functioning in the period after resolution of acute depression and that this differential treatment effect had taken some time to develop.

Puig-Antich et al. (11) also reported on social adjustment assessed 4 months or more after recovery from an episode of major depression in prepubertal children treated with imipramine. School functioning was found to be completely normalized; however, deficits in interpersonal relationships had improved only partially. The authors suggested that these residual deficits might either resolve spontaneously over a longer period or might be amenable to an adjunctive psychotherapeutic intervention.

Our study addressed a distinctive sample of depressed patients in that all subjects had been depressed for at least 2 years and the average reported duration of depression was 20 years. Six weeks of imipramine treatment produced greater improvement than placebo in measures of social-vocational function; however, during this time period, few patients achieved a level of adjustment comparable to published norms for a community sample (6). It is therefore important to extend this research about antidepressant drug treatment of chronic depression to larger samples on whom assessments are carried out over longer periods to determine the maximum degree of benefit that can be obtained. The potential benefits of adjunctive psychotherapeutic interventions should also be explored in future studies involving chronic depression.

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DSM-III, Draft *DSM-III-R*, and the Diagnosis and Prevalence of Bulimia in Australia

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A self-report questionnaire for bulimic symptoms was administered to three different groups of community residents and to patients in a hospital's weight disorders unit and its dietetics department. The prevalence of DSM-III *bulimia was 12.7% among female community residents, while the prevalence of draft* DSM-III-R *bulimia was 1.7%. The questionnaire, scored to reflect* DSM-III, *categorized as bulimic large numbers of patients who were not given that diagnosis by clinicians. The draft* DSM-III-R *criteria seemed more closely aligned to clinical experience.*

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There has been an extraordinary proliferation of writing and research into bulimia since *DSM-III* was first published. In the years since 1980, bulimia has gone from being virtually unknown (1–3) to being described by some medical investigators as a "major public health problem" (4) and being designated by at least one prominent nonmedical leader of contemporary female opinion as a disorder of "epidemic proportions" (5).

A more cautious view of the current epidemic of bulimia is that the diagnostic criteria for bulimia put forward in *DSM-III* are somewhat broad (6). There is a danger that, when used alone to categorize subjects in epidemiological studies, they may tend to identify as bulimic large numbers of individuals whose behavior does not actually resemble that of patients in treatment for the disorder (7, 8). It is possible, therefore, that the current perception of an epidemic of bulimia may to some extent be iatrogenic in origin.

Draft proposals for *DSM-III-R* were published in 1985. The suggested criteria for the diagnosis of bulimia vary substantially from those put forward in *DSM-III*. Since 1984 I have been conducting a series of linked studies examining the prevalence of bulimic symptoms and syndromes in clinic and community populations in South Australia. It has been possible to use the data to examine the impact on diagnosis and prevalence of the changes put forward by the authors of the draft *DSM-III-R*.

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METHOD

Halmi et al. (9) have published a self-report questionnaire for bulimic behavior. It was amended by adding questions related to the frequency of binge eating, the kinds of food consumed during binges, and the use of fasting for weight control. The questionnaire's test-retest reliability was established by administering it to a group of 20 hospital employees on two occasions over a 3-week period (Spearman's rho=0.98, N=20, $p<0.001$).

Three community groups were then studied by using the questionnaire. The groups included shoppers in a suburban shopping center (4), female patients at a family medicine practice located opposite the shopping center, and students at the public high school serving the suburb in which the shopping center and family medicine practice were located. The shopping center sample comprised one in six shoppers passing through one of the shopping center entrances, sampled throughout the shopping day over a 1-week period. A total of 589 shoppers were approached, and the response rate was 66% (N=389). This group filled out a short form of the questionnaire, which omitted questions about diet pills, laxatives, and fasting. The family practice group comprised consecutive female patients over a 4-day period; 234 patients were approached, and a response rate of 94% (N=220) was obtained. For the high school study, the questionnaires were given out to the whole high school during one school period. There was a 74.1% response rate from the school's 1,069 pupils (N=792).

Two clinical groups were also studied with the questionnaire: a consecutive sample of all 80 patients referred for initial outpatient assessment to a university hospital's specialized weight disorders unit (10) over a 1-year period and 31 consecutive subjects in the same

hospital's dietetics department over a 2-month period. Most of the women in the dietetics group were mildly or moderately obese and were seeking advice about weight reduction. The dieticians were familiar with the varied presentations of anorexia nervosa and bulimia and were asked to exclude all such patients from the dietetics sample. All patients approached agreed to participate in the study.

All responses were anonymous. No respondent was paid for participation.

RESULTS

Seventy-eight of the 80 patients seen in the weight disorders unit during the study period were women. The remainder of this report is confined to female subjects only. The weight disorders unit has been using *DSM-III* for some years. The clinical diagnoses of the unit's patients were as follows: bulimia (N=27), anorexia nervosa (N=31), and atypical eating disorders (N=20). Eleven of the patients given a diagnosis of atypical eating disorders were described by clinicians as having mild anorexia, i.e., they fulfilled all the *DSM-III* criteria for anorexia nervosa except that their weight loss had not reached 25%. The remainder of the patients in the atypical group were designated by clinicians as having atypical bulimia and included overweight patients with bulimic eating patterns; patients who repetitively binged and then spat out ingested food; and patients with complex weight, eating, and behavioral difficulties. Seven of the nine patients with atypical bulimia and 26 of the 27 diagnosed bulimic patients vomited and/or used laxatives to rid themselves of ingested food.

Female subjects' questionnaire responses were used to allocate them to one or more of the following diagnostic groups: *DSM-III* bulimia, *DSM-III* bulimia with monthly binge vomiting, and draft *DSM-III-R* bulimia. Allocation was made by determining whether subjects' responses fulfilled predetermined criteria for each diagnosis.

For *DSM-III* bulimia, subjects had to respond positively to questions that tested whether they fulfilled the following *DSM-III* criteria: A. recurrent episodes of binge eating (rapid consumption of a large amount of food in a discrete period of time, usually less than 2 hours); B. (1) consumption of high-caloric, easily ingested food during a binge, (2) inconspicuous eating during a binge, and (3) frequent weight fluctuations greater than 10 pounds due to alternating binges and fasts; C. awareness that the eating pattern is abnormal and fear of not being able to stop eating voluntarily; and D. depressed mood and self-deprecating thoughts following eating binges.

DSM-III bulimia with monthly binge vomiting was, as its title suggests, *DSM-III* bulimia as defined earlier, as well as binge eating and inducing vomiting at a minimum level of once per month; no maximum frequency of binge eating or vomiting was prescribed.

For draft *DSM-III-R* bulimia, subjects had to respond positively to questions that directly tested whether they fulfilled the following criteria: A. recurrent episodes of binge eating (rapid consumption of a large amount of food in a discrete period of time, usually less than two hours); B. during the eating binge there is a feeling of lack of control over the eating behavior; and C. the individual regularly engages in either self-induced vomiting, use of laxatives, or rigorous dieting or fasting in order to counteract the effects of the binge eating. Because subjects had not been asked for how long they had been binge eating, it was possible to only partially test for criteria D.: a minimum average of two binge-eating episodes per week for at least three months. However, subjects were allowed to qualify as having a diagnosis of draft *DSM-III-R* bulimia by fulfilling criteria A, B, and C and a modified D in which the frequency but not the duration element had to be satisfied. At least in the clinical setting, all the bulimic subjects who had episodes of binge eating twice a week had had such a pattern for many months, and it was thought unlikely that the use of a partial criterion would lead to any substantial distortion.

The diagnosis of anorexia nervosa precludes a simultaneous diagnosis of bulimia in *DSM-III*. Because no adequate questionnaire measure of anorexia was available, that exclusion criterion could not be used when community subjects were categorized as having bulimia. A total of 11.8% of the family practice group (N=26), 15.2% of the girls in the high school group (N=54), and 10.0% of the women in the shopping center group (N=33) fulfilled the *DSM-III* criteria for bulimia (overall prevalence, 12.7% [N=113]). A total of 0.5% of the family practice group (N=1), 0.3% of the high school group (N=1), and 1.3% of the shopping center group (N=4) fulfilled the *DSM-III* criteria for bulimia with monthly binge vomiting (overall prevalence, 0.67% [N=6]). A total of 1.4% of the family practice patients (N=3) and 2.0% of the high school group (N=7) fulfilled draft *DSM-III-R* criteria for bulimia, for an overall prevalence of 1.7% (N=10) of the eligible population.

The criteria in *DSM-III* have often been the sole arbiter of diagnosis in epidemiological studies using self-report measures (9, 11–14). In table 1, clinical diagnoses are compared with the various diagnoses made by use of the self-report questionnaire. If the patients in the weight disorders unit who were diagnosed as bulimic by clinicians were taken to represent true cases of bulimia, and if patients diagnosed as having atypical bulimia and the dietetics patients were taken to be true noncases, then the self-report questionnaire, when scored strictly to accord with the *DSM-III* criteria, had a sensitivity (proportion of true cases correctly identified) of 100% but a specificity (proportion of true noncases correctly identified) of only 62.7%. The false positive diagnostic rate was 42%, and there were no false negative diagnoses. Diagnostic questionnaires that use adherence to *DSM-III* criteria as the sole in-

TABLE 1. Prevalence of Bulimia Among Patients Evaluated for Eating Disorders in Australia

Group	N	*DSM-III* Bulimia		*DSM-III* Bulimia With Monthly Binge Eating and Vomiting		Draft *DSM-III-R* Bulimia	
		N	%	N	%	N	%
Weight Disorders Unit							
Bulimia	27	27	100.0	23	85.2	18	66.6
Anorexia nervosa	29	10	34.5	5	17.2	1	3.4
Atypical eating disorders	20	10	50.0	4	20.0	4	20.0
Dietetics department	31	9	29.0	2	6.5	2	6.5

dex of diagnosis are likely (7) to include as bulimic large numbers of individuals who would not be so diagnosed by clinicians.

Only 18 of 27 patients diagnosed as bulimic fulfilled the draft *DSM-III-R* criteria. Those criteria are therefore likely to lead to the recategorization of some individuals currently in treatment for bulimia. However, far fewer nonbulimic patients would be likely to be incorrectly labeled as bulimic if the draft *DSM-III-R* criteria were to be used to calibrate diagnostic questionnaires.

DISCUSSION

A total of 12.7% of women in a community sample could be diagnosed as bulimic according to the *DSM-III* criteria, but only 1.7% fulfilled the draft *DSM-III-R* criteria for bulimia. The latter criteria have been incorporated, virtually unchanged, into the criteria for bulimia nervosa in the final *DSM-III-R*. The use of *DSM-III-R* seems likely to lead to a dramatic decline in the diagnosis and prevalence of bulimia.

The change in rates of bulimia between *DSM-III* and draft *DSM-III-R* occurred because of a tightening of diagnostic criteria. The criteria for the diagnosis of bulimia in draft *DSM-III-R* require not only binge eating but self-induced vomiting or use of other means to rid oneself of ingested food after binge eating. Furthermore, the draft *DSM-III-R* added frequency and duration criteria that require a minimum of two binge-eating episodes per week for at least 3 months. To a large extent, those elements accorded well with our own clinical experience and that of others (3, 6, 7). In this study 33 of 36 patients in treatment for either bulimia or an atypical eating disorder with a prominent bulimic element vomited or used laxatives to rid themselves of food ingested during a binge, and those behaviors had been of longstanding duration.

The incorporation of draft *DSM-III-R* or *DSM-III-R* diagnostic criteria into self-report questionnaires should lead to an increase in diagnostic specificity in comparison to measures using *DSM-III*. A self-report questionnaire, scored to identify cases by *DSM-III* criteria alone, identified as bulimic a substantial number of subjects who were not diagnosed as bulimic by clinicians who knew them well. By contrast, the draft *DSM-III-R* criteria seemed much more closely aligned to clinical practice, although their rigorousness may eventually lead to a degree of "specificity overshoot." For instance, one-third of the patients in this study who were diagnosed as bulimic by clinicians failed to meet the criteria for binge frequency of the draft *DSM-III-R*. There is thus a danger that the draft and definitive *DSM-III-R* will not do justice to those individuals who require professional help for an eating disorder yet whose problems are "subdiagnostic" in intensity.

Some kind of compromise between *DSM-III* and draft *DSM-III-R* might eventually provide a reasonable balance between diagnostic sensitivity and diagnostic specificity. However, much more experience will have to be gained before a clear picture emerges.

Overall, it is clear that any epidemic of bulimia in the community, as ascertained by self-report questionnaires that use *DSM-III*, is not an epidemic of problems of clinical severity. The evidence mounts that bulimic behavior which is comparable in breadth and severity to that found in clinical settings only occurs in 1% to 2% of women in general. That is not a small problem, but it also is not an epidemic.

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Case Review and Quantity of Outpatient Care

Barry Blackwell, M.D., Mary Gutmann, Ph.D., and Lily Gutmann, B.A.

Case review for patients belonging to a health maintenance organization was implemented in a hospital-based, multidisciplinary, outpatient clinic after the influx of 28,000 Medicaid enrollees. One-year follow-up of 138 patients with prepaid mental health insurance and 283 patients with fee-for-service mental health insurance revealed an annual mean of 6.1 treatment sessions; 78% completed treatment within eight sessions. The modal treatment was a single visit. Prepaid and fee-for-service patients did not differ in amount of care, although significant differences were found for insurance subgroups. These preliminary results suggest that case review has little effect on quantity of care.

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Over the past 15 years the number of health maintenance organizations (HMOs) has grown from 33 in 1970 to 480 in 1985, almost a 15-fold increase (1). The growth has been exponential, the largest increase (26%) occurring in the past year. Although the impact on mental health services has been profound, it is also disturbing because radical change has occurred in the absence of reliable information. Two surveys of prepaid mental health services have been published, one conducted in 1980 (2) and the other in 1982 (3). A handful of studies have reported more specific data (4–9), but at a recent NIMH conference representatives from nine typical HMOs arrived at a consensus that "at present there are no cumulative data on HMO mental health services—on the numbers and types of patients seen, length of treatment, modalities of care provided, costs, staff size and composition, referral patterns and the like" (10).

This preliminary report describes a situation in which an academic department of psychiatry in an urban general hospital was confronted with the need to manage a sudden large influx of patients with prepaid mental health insurance under a system of separate mental health capitation that placed the hospital at financial risk. As pointed out in a recent review of capitation and mental health care (11), "disappointingly little empirical information about the impact of capitation on the quality of care is available." This lack of information coupled with the absence of rational criteria for allocation of psychotherapy posed the difficult clinical and ethical issues of how to manage services without sacrificing quality of care. This dilemma led in turn to the adoption of a system of case review that required pretreatment authorization and limited the number of sessions approved. Our study retrospectively describes the impact of the case review system during the first 18 months of its operation on the amount of treatment provided to prepaid (HMO) patients and compares it to the amount of care provided to fee-for-service patients (treated without restriction) by the same therapists in a multidisciplinary outpatient clinic.

METHOD

In 1984, the Wisconsin Department of Health and Social Services enrolled over 110,000 recipients of Title XIX Aid to Families with Dependent Children (AFDC) recipients who lived in Milwaukee county into HMOs. Mount Sinai Medical Center suddenly assumed responsibility for providing care to 28,000 of these individuals through contracts that provided a fixed capitation (dollar amount per member per month) to cover all "medically necessary" services defined as the presence of an *ICD-9-CM* diagnosis.

The Mount Sinai Medical Center is a 300-bed general hospital in downtown Milwaukee that serves as the Milwaukee clinical campus of the University of Wisconsin School of Medicine. The outpatient clinic has a multidisciplinary staff consisting of 12 master's level psychiatric social workers, three psychiatrists, three psychologists, and trained counselors in alcohol and drug abuse. The professional staff are divided into treatment teams supervised by a psychiatrist and coordinated by a psychotherapist. The staff utilizes a range of treatment modalities (individual, group, or family) and approaches (psychodynamic, behavioral, or pharmacologic).

The clinic provides over 1,500 visits a month to an annual caseload of 800 patients. Of the 421 new patients entering treatment between January and June 1985, 138 (33%) were enrolled in prepaid HMOs of which 84 (61%) were Title XIX AFDC recipients.

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Two-thirds (N=283) were fee-for-service patients: 46% (N=130) had indemnity insurance, 19% (N=54) had Medicaid insurance, 21% (N=60) had Medicare insurance, and the remainder (14%, N=39) were indigents covered by county welfare funds. Thus, 54% (N=153) of the fee-for-service and 61% (N=84) of the prepaid patients receive some type of public assistance.

The mean±SD age of the 421 new patients was 39±16 years; 72% (N=303) were women, and 27% (N=114) were black. Diagnostically, 41% (N=173) had neurotic disorders, 20% (N=84) had adjustment disorders, and 17% (N=72) had psychotic conditions. Personality disorders were diagnosed in 11% (N=46), and 13% (N=55) had alcohol or drug problems; organic conditions were noted in only 2% (N=8). Diagnostic groups were similar for prepaid and fee-for-service patients with three exceptions: The prepaid group had a significantly higher frequency of substance abuse (18% versus 10%; $\chi^2=4.24$, df=1, $p<0.05$), a lower prevalence of neurotic disorders (29% versus 48%; $\chi^2=11.39$, df=1, $p<0.001$), and a higher prevalence of adjustment disorders (31% versus 13%; $\chi^2=17.06$, df=1, $p<0.001$).

Although nothing was known about the prevalence of psychiatric problems or utilization patterns of the 28,000 prepaid members, who consisted largely of lower socioeconomic, predominantly black, single mothers and their children, we were mandated to provide all "medically necessary" care within a fixed budget by psychotherapists accustomed to open-ended and not time-limited forms of therapy. For ethical, clinical, and financial reasons, it became essential to develop a system that would determine the medical necessity for treatment, encourage cost containment, monitor quality of care, and provide an accurate database to evaluate the system's overall impact.

A quality-monitoring committee was set up consisting of the chief of the department (B.B.), the senior psychologist (M.G.), the director of child psychiatry, and an HMO coordinator from the Office of HMO Affairs, which manages the financial and contractual arrangements between the medical center and the HMOs. This committee met weekly and also once a month with the psychotherapists and administrative staff in the outpatient clinic.

Forms devised for initial treatment plan approval and for subsequent updates included demographic data, presenting problems, diagnoses, and the goals, methods, expected frequency, and duration of treatment. Every prepaid patient was required to have prior authorization for treatment. Approval of the initial evaluation for eight 1-hour sessions (and up to four additional 15-minute medication checks) is given routinely provided that the treatment is deemed medically necessary, the form is legible, and the goals and treatment plans are considered appropriate. Requests for additional treatment are submitted on update forms and are rigorously reviewed for necessity and appropriateness. If a reviewer has concerns, these are dealt with by telephone contact or at the regular monthly meetings in the clinic.

A retrospective review was made of adult patients who entered treatment from January through June 1985 and were followed for 12 months after the first clinic contact. During this time, all prepaid patients and their therapists were subjected to the case review procedures while all fee-for-service patients were treated in a traditional, open-ended, and not time-limited manner.

Data were obtained from clinic records and chart audits. The number of sessions represents amount of treatment provided over 12 months from time of intake. Cost of services was calculated on the basis of standard fees charged for number of units (one unit=15 minutes) and purpose of service (evaluation, therapy, or medication). Mean±SD, median, and mode were calculated on the number of sessions and cost over 12 months for the entire sample and for each insurance type. Analysis of variance (ANOVA) on mean number of sessions was done for all six insurance groups and for the four fee-for-service groups. Post hoc t tests were performed for significant F values ($p\leq0.05$). Comparisons between the two major insurance groups (fee-for-service and prepaid) were also done by means of t tests. The proportion of patients with single sessions or greater than 16 sessions were compared for various insurance groups by means of chi-square tests. A two-tailed probability of 0.05 or less was considered significant for all statistical values.

RESULTS

A total of 421 patients entered treatment. One-third (138 or 33%) were patients in prepaid HMOs subjected to case review, and two-thirds (283 or 67%) were fee-for-service patients. The amounts and cost of care for the different insurance groupings are shown in table 1. Overall, patients were treated for an average of six sessions at a mean annual cost of $462. The modal treatment was a single visit (32% of all patients); 78% concluded therapy in less than eight sessions, and only 9% received more than 16 sessions.

Analysis of utilization within the insurance types revealed two major findings. The first was that overall there is no major difference between prepaid and fee-for-service patients in the amount (t=0.46, df=419) or cost (t=0.51, df=419) of care provided. The only significant difference between the groups was that more fee-for-service patients (36.4%) than prepaid patients (22.5%) were seen once only (table 1). There was a nonsignificant tendency for more fee-for-service patients (10%) than prepaid patients (7%) to receive extended treatment (over 16 sessions) ($\chi^2=1.57$, df=2). Second, ANOVA and post hoc t tests revealed significant differences in mean number of treatment sessions among all types of insurance and within the major fee-for-service and prepaid categories (F=5.49, df=5, 415, $p<0.001$). Within the fee-for-service groups

TABLE 1. Amount and Cost of Treatment for 138 Patients in Prepaid HMOs and 283 Fee-for-Service Patients

Insurance Type	Treatment Sessions per Year			Treatment Sessions Attended								Mean Cost per Month ($)
				1		≤8		9–16		>16		
	Mean	SD	Median	N	%	N	%	N	%	N	%	
All patients (N=421)	6.1	6.9	3.3	134	31.8	327	77.7	56	13.3	38	9.0	462
Fee-for-service (N=283)	6.0	7.5	3.0	103	36.4[a]	223	78.8	31	11.0	29	10.2	454
County welfare (N=39)	8.0	8.9	4.8	10	25.6	29	74.3	3	7.7	7	17.9	594
Title XIX (N=54)	4.6[b]	5.3	3.0	19	35.2	44	81.5	8	14.8	2	3.7	401
Medicare (N=60)	3.1[c]	4.1	1.0	38	63.3	55	91.7	4	6.7	1	1.7	281
Commercial (N=130)	7.3	8.6	4.5	36	27.7	95	73.1	16	12.3	19	14.6	513
Prepaid (N=138)	6.3	5.5	4.9	31	22.5	104	75.4	25	18.1	9	6.5	479
Commercial (N=54)	8.0[d]	5.8	6.6	7	13.0	35	64.8	15	27.8	4	7.4	575
AFDC (N=84)	5.2	5.1	3.6	24	28.6	69	82.1	10	11.9	5	6.0	417

[a]Significantly more than for prepaid patients (χ^2=8.30, df=2, p<0.02).
[b]Significantly fewer than for county welfare patients (t=2.32, df=91, p<0.05) and fee-for-service commercial patients (t=2.11, df=182, p<0.05).
[c]Significantly fewer than for county welfare patients (t=3.73, df=97, p<0.001) and fee-for-service commercial patients (t=3.57, df=188, p<0.001).
[d]Significantly more than for AFDC patients (t=3.57, df=188, p<0.001).

(table 1), Title XIX patients had significantly fewer mean number of visits per year than the indigent patients on county welfare and the indemnity commercial insurance patients. Medicare recipients had the lowest utilization rate with significantly fewer mean sessions per year than county welfare patients and fee-for-service commercial patients but not Title XIX patients (t=1.71, df=112). Within the prepaid plans, the commercial patients (enrolled in an Independent Practice Association) had significantly more treatment sessions per year compared to AFDC recipients enrolled in the same HMOs.

DISCUSSION

The introduction of a case review system did not significantly alter the amount of treatment received by prepaid patients compared to fee-for-service patients. This is surprising because the assumption is often made that HMO procedures serve to restrict access or ration care, leading to considerable ethical debate in both general medical (12) and psychiatric (13) journals. This concern persists despite the conclusions of the Rand Health Insurance Studies (14) and a variety of comparisons of surgical and medical care (15) that consistently find either better or no worse care in HMO than in fee-for-service populations. Case review has been introduced into the HMO setting for cost containment and quality-monitoring purposes (16), but its impact on the amount and type of service has not been reported.

The lack of difference we found is particularly meaningful because treatment was provided to both groups of patients by the same therapists who were accustomed to providing open-ended and not time-limited therapy and who had serious misgivings about what they perceived as a form of rationing. They were also concerned that patients would complain about receiving less than the expected amount of care. The arbitrary imposition of an eight-session limit on pretreatment authorization is below the 20 sessions provided for in the original federal HMO legislation and still allowed for in over three-quarters of national organizations (3). After almost 2 years of experience, these concerns have largely dissipated, and an independent review of patient satisfaction by one of our HMOs produced no complaints.

Our data also reveal some statistically significant differences in amount of care consumed within different insurance categories. Similar unexplained sources of variance in amounts of care consumed are well described in the literature (17) and are the major reason for concern among insurers that has led to the strategy of separate capitation. However, these variances, while occasionally statistically significant, are of manageable proportions because the majority of patients who seek outpatient mental health care require short-term therapy. This finding is surprising to many mental health professionals, particularly those in private practice who, until now, have mostly treated selected samples of patients who need, are interested in, or are able to pay for longer term treatment. The existence of separate capitation may encourage the referral of individuals who have previously been treated at even lower cost by general medical practitioners (18). A growing consensus in the literature indicates that in most HMO settings the mean number of treatment sessions per episode is between three and 12 and the modal number is from one to three (5–7, 10); thus, the major reason why our case review system had no impact on quantity of care may be that quantity of care is largely determined by the short-term natural history of most outpatient mental health problems.

Our results apply only to adults and not to children or adolescents who may require substantially more care or who might react differently to a case review system. Samples with a different mix of patients or welfare recipients might also differ, and our system was applied essentially in a closed panel setting and

may be less applicable in private practice. Also, quantity of care provided is a relatively crude measure of quality, which may be impaired in subtler ways in prepaid care by case review procedures.

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Growth Hormone Response to Edrophonium in Patients With Alzheimer's Disease and Normal Control Subjects

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The authors found that growth hormone (GH) response to edrophonium was no different in 12 Alzheimer's disease patients than in eight healthy elderly subjects. Previously reported differences could be due to differences in gender or baseline GH concentrations between patients and control subjects.

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Alzheimer's disease is characterized by substantial losses of cholinergic activity within the CNS, including the hypothalamus (1). The characteristic neurofibrillary changes of Alzheimer's disease involve the median eminence. Pituitary growth hormone (GH) secretion is powerfully regulated by acetylcholine (2), an action that occurs outside of the blood-brain barrier (presumably in the pituitary or median eminence).

The neurobiology involved in the response of GH to a cholinesterase inhibitor has been discussed elsewhere (3, 4). Since the administration of peripheral cholinesterase inhibitors increases plasma GH in human subjects, patients with Alzheimer's disease might have a reduced supply of acetylcholine in areas controlling GH secretion; therefore, cholinesterase inhibition with edrophonium might result in a reduced GH response. This hypothesis was tested in a group of Alzheimer's disease patients who demonstrated a markedly reduced GH response to edrophonium challenge compared to the response of control subjects (4). The present study attempts to replicate this finding while considering somatic and physiological variables known to influence GH secretion.

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METHOD

The study sample consisted of seven male patients with Alzheimer's disease, age 55–72 years (mean±SD, 63.9±8.1 years), five Alzheimer's disease female patients, age 56–71 years (mean±SD, 64±6.1 years), four healthy male volunteers, age 55–76 years (mean ±SD, 67±9.1 years), and four healthy female volunteers, age 59–63 years (mean±SD, 62±2.5 years).

All patients and control subjects gave written informed consent to participate in the study, were free of all medical illnesses, and had not taken drugs for at least 2 weeks before the study began. Diagnosis of "probable Alzheimer's disease" was made according to National Institute of Neurological and Communicative Disorders and Stroke criteria (5). A score higher than 4 on the Hachinski scale or any CT scan abnormality, except for generalized cortical atrophy, was reason for exclusion from the study. Severity of dementia was assessed with the Memory and Information Test, the Blessed-Roth Dementia Scale, and Dementia Rating Scale.

The patients and the control subjects were admitted at least 24 hours before the study and slept in the study room. They had nothing to eat or drink, did not smoke, and had complete bed rest for 12 hours before and throughout the study. An intravenous catheter was inserted at 8:00 a.m., and blood for GH was sampled at 10-minute intervals until 1:00 p.m. Edrophonium, 0.15 mg/kg of body weight, or saline (placebo) was injected intravenously at 10:00 a.m. Drug and placebo were given 1 week apart in a randomized fash-

TABLE 1. GH Concentrations Before and After Edrophonium Administration in Patients With Alzheimer's Disease and Normal Control Subjects

	GH Secretion (ng/ml)					
	Baseline		Peak		Total	
Subjects	Mean	SD	Mean	SD	Mean	SD
Alzheimer's disease (N=12)						
Men (N=7)	1.6	1.0	5.3	4.8	45.8	28.7
Women (N=5)	1.6	1.0	1.1	0.9	25.8	7.9
Normal control (N=8)						
Men (N=4)	1.2	0.1	10.1	4.9	70.7	32.5
Women (N=4)	1.8	0.5	1.7	1.5	26.9	10.3

ion. Patients and control subjects occasionally reported transient teariness and stomach grumbling. No clinically significant arrhythmias or blood pressure changes were observed.

Baseline GH was considered to be the average of GH values sampled between 9:40 and 10:00 a.m. before edrophonium was administered. GH response to edrophonium was evaluated by calculating 1) the total GH secretion after edrophonium and 2) peak GH concentrations. Total GH secretion was considered to be the sum of GH values sampled between 10:10 a.m. and 1:00 p.m. Peak GH concentration was obtained by subtracting the baseline values from the highest GH values measured any time between 10:10 a.m. and 1:00 p.m. Intra- and interassay coefficients of variation for the GH assay were 6% and 14%, respectively.

RESULTS

The mean±SD GH values for men and women in both groups are given in table 1. A two-way ANOVA demonstrated that edrophonium-stimulated peak GH concentrations did not differ between Alzheimer's disease patients and control subjects ($F=2.73$, $df=1, 16$, $p<0.12$); however, male subjects had significantly greater peak GH concentrations than did female subjects ($F=12.09$, $df=1, 16$, $p<0.003$). There was no interaction between diagnostic group and sex ($F=1.52$, $df=1, 16$, $p<0.23$). Similar to peak GH concentrations, total GH secretion after edrophonium administration did not differ between Alzheimer's disease patients and control subjects ($F=1.67$, $df=1, 16$, $p<0.21$) but did differ between men and women ($F=7.9$, $df=1, 16$, $p<0.012$), and there was no interaction between diagnostic group and sex ($F=1.23$, $df=1, 16$, $p<0.28$).

There were no significant correlations between severity of illness as assessed by the Memory and Information Test, Dementia Rating Scale, and Blessed-Roth scale scores and any of the measurements of GH secretion. Age did not correlate with GH secretion.

DISCUSSION

Our data do not corroborate the reported difference in edrophonium-stimulated GH secretion between normal subjects and patients with Alzheimer's disease (4). We found that gender was the major factor influencing edrophonium-stimulated GH levels: Men had higher concentrations than women, a finding that has been documented in literature (6). Elderly men have also been reported to have a greater GH response to insulin-induced hypoglycemia and to apomorphine stimulation than do elderly women (7). We cannot compare our data on gender with data from the previous report (4), because that study did not specify the gender of the subjects.

The most likely explanation for the lower GH response to edrophonium in Alzheimer's disease patients than in control subjects reported previously (4) is their unusually high baseline GH concentrations, which is in contrast to our finding of lower, apparently normal, baseline GH concentrations in our patients with Alzheimer's disease. High baseline GH concentrations are known to blunt GH response to pharmacological challenges (8, 9). In a recent apomorphine stimulation study, the validity of the conventional 5 ng/ml cutoff for baseline GH concentration was examined; only one of seven subjects with a baseline GH concentration of higher than 5 ng/ml during the 45 minutes before apomorphine challenge had a GH response of higher than 10 ng/ml, and 23 of 33 subjects with normal baseline concentrations had GH responses from 10 to 68 ng/ml (B. Davis, K. Davis, R.C. Mohs, et al., unpublished data). GH inhibition by prior secretion is also seen when high doses of growth hormone-releasing factor (GH-RF) are administered. A biphasic GH response is obtained, with the smaller, second peak occurring 75–105 minutes after the first, despite the presence of plasma GH-RF concentrations capable of stimulating GH release throughout this time period (8). Similarly, the increments in GH peripheral concentrations produced by L-dopa are followed by a refractory interval (9). Thus, in the previous study (4), the mean baseline GH concentration of 6.0±7.3 ng/ml in the Alzheimer's disease patients suggests that many had concentrations higher than the cutoff of 5 ng/ml and probably accounts for their subsequently blunted GH response to edrophonium, which was not observed in the normal subjects, who did not have elevated baseline GH concentrations.

Other factors that cannot be directly assessed but may explain our differing results include whether the subjects were inpatients or outpatients, whether they were fasting, or whether they were allowed to smoke before the study. Each could potentially contribute to the observed GH differences, but this information was not presented in the previous study (4).

It is not clear that a cholinesterase inhibitor will produce less acetylcholine release (and presumably less GH secretion) in the Alzheimer's disease than in the normal brain. In fact, physostigmine increased acetyl-

choline release from Alzheimer's disease and control brain slices obtained at autopsy to the same level (10). The normal GH release after edrophonium administration observed in this study suggests that cholinergic transmission may be normalized by a cholinesterase inhibitor. Normalization of neuroendocrine and biochemical cholinergic processes in the brains of Alzheimer's disease patients by a cholinesterase inhibitor raises hope that cognitive function in patients may be similarly improved by cholinesterase inhibitors that can reach the target cells in adequate concentrations and for a useful period of time.

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Effect of Sodium Valproate in Three Patients With Organic Brain Syndromes

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Three patients with organic and affective symptoms related to multiple sclerosis or systemic lupus erythematosus responded dramatically to sodium valproate after other treatments had failed.

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Sodium valproate, an anticonvulsant, has been reported to be effective in bipolar and schizoaffective disorders (1, 2). The finding that patients with nonparoxysmal EEG abnormalities responded better than others to this drug (2) suggested to us that valproate might be useful for agitated patients with organic brain syndromes. We report here the treatment of three such inpatients admitted to our medical-psychiatric unit. Two of the patients had multiple sclerosis and the third had systemic lupus erythematosus.

CASE REPORTS

Case 1. Ms. A, a 50-year-old previously healthy woman with a family history of bipolar disorder, was admitted to the hospital because of acute onset of hemiparesis, ataxia, and delirium, with confusion, agitation, insomnia, depression, and psychosis. A magnetic resonance imaging scan of the brain showed demyelinated plaques, visual evoked potentials were abnormal, and oligoclonal bands were present in the CSF. An EEG showed diffuse slowing. Ms. A was given diagnoses of multiple sclerosis and secondary delirium with depressive features. Her motor symptoms cleared over the course of 4 weeks without the use of steroids. For the delirium, chlorpromazine, 150 mg/day for 9 weeks, had no effect other than sedation; higher doses provoked rigidity. Desipramine, administered concurrently for 7 weeks (maximum dose, 250 mg/day; blood level, 496 ng/ml), had no effect. When valproate, 250 mg t.i.d., was added, Ms. A's mood and level of awareness improved within 24 hours. Within 9 days all of her symptoms had resolved. The patient spontaneously described the improved clarity of her thinking. Her blood level of valproate on day 10 was 73 mg/liter. She was discharged while still taking all three medications (without major change in blood levels of desipramine), since we were not sure, at the time, which was the curative agent. At 4-month follow-up she remained well.

Case 2. Ms. B, a 43-year-old woman, had a 10-year history of primary bipolar disorder with yearly cycles. She complied poorly with her lithium therapy regimen. Eighteen months before the hospital admission that we shall describe, she presented with mania and the simultaneous acute onset of multiple sclerosis with quadriparesis. The laboratory findings were the same as in case 1. She received no steroids after an initial course that left her with residual ataxia and mild dementia. Thereafter, her psychiatric course worsened despite her compliance with the lithium regimen (lithium levels of 0.7–0.9 meq/liter); she had frequent hospitalizations due to rapid cycling accompanied by delirium, the latter exacerbated by high doses of lithium or neuroleptics. She was given carbamazepine during one manic phase, but the medication was stopped because she had an allergic reaction.

On admission to our hospital, Ms. B had psychotic mania and delirium, with severe confusion, insomnia, and belligerence. Her lithium level was 1.0 meq/liters. She was too uncooperative for repeat neurological laboratory studies to be made; however, no new focal deficits were seen on examination. She showed no response to 2 weeks of treatment with trifluoperazine, 32 mg/day, benztropine, 4 mg/day, and clonazepam, 6 mg/day, plus lithium up to a blood level of 1.5 meq/liter for the first week. She developed severe ataxia, extrapyramidal rigidity, and increasing fluctuations in consciousness. Treatment with valproate, 250 mg t.i.d., was begun. Following the fourth dose, Ms. B became profoundly sedated, and all drugs were stopped. Her manic symptoms reemerged within 48 hours, but her consciousness was clearer. Treatment with valproate alone, at a dose of 250 mg b.i.d., was restarted. She slept normally the first night and within 2 days became cooperative, oriented, and coherent. Her ataxia returned to its baseline level. Over the course of a week her mood and psychosis cleared as the dose of valproate was increased to 250 mg t.i.d. (blood level, 95 mg/liter). At 4-month follow-up, Ms. B remained well except for mild cognitive impairment.

Case 3. Ms. C was a 29-year-old woman who had had systemic lupus erythematosus for 7 years and had a 5-year history of mania and depression. Her affective episodes were presumed to be secondary to the lupus, as they coincided with flare-ups of fever, arthralgia, butterfly facial rash, and elevated erythrocyte sedimentation rate. Only one episode was preceded by increased steroids. Her apparent lack of focal neurological deficits was unconfirmed, since she repeatedly refused to have an EEG or a CT scan. For the past 2 years she had taken lithium (lithium levels were 0.9–1.1 meq/liter), with both a manic and a depressive breakthrough; she

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had been euthymic for 8 months, after the addition of desipramine, 200 mg h.s., to her regimen. She was also taking prednisone, 5 mg/day, and methotrexate, 7.5 mg once weekly.

One week before admission to the hospital, Ms. C abruptly developed a flare-up of her lupus condition, with psychotic mania and confusion. She was hospitalized after she did not respond to the cessation of desipramine, an increase in her doses of lithium and prednisone, the addition of thioridazine and clonazepam to her regimen, and one dose of methotrexate. In the hospital she remained unchanged for 3 days while taking only prednisone, 7 mg/day, and thioridazine, 150 mg h.s. Valproate was then started at a dose of 250 mg/day. Within 48 hours there was improvement in her impulsivity and concentration, which was described by her skeptical internist as "gratifying." Correlating with increases of her dose of valproate over 1 week to 1250 mg/day (blood level, 96 mg/liter), her mood steadily returned to normal. As her physical lupus symptoms continued to flare, however, her internist wanted her to resume taking methotrexate. Fearing a toxic bone marrow interaction with an unfamiliar drug, he requested that the valproate be tapered. During a 3-week taper, Ms. C became progressively manic despite continuing to take prednisone, 7 mg/day, and thioridazine, 150 mg h.s., and resuming weekly doses of methotrexate.

DISCUSSION

All three patients responded to valproate rapidly and without side effects after trials of other medications had failed. We attribute the differential response to the presence of organic illness. Alternatively, it is possible that our patients, especially Ms. B, had primary affective illnesses that were just refractory to standard treatment. None of the patients had seizures, nor was there an effect of valproate on the underlying medical illnesses.

Psychiatric symptoms and cognitive deficits are seen in most patients with severe multiple sclerosis (3) and systemic lupus erythematosus (4). Affective symptoms in multiple sclerosis appear to be the result of structural brain lesions rather than simply psychological reactions to illness (5). In lupus, psychosis and affective illness may result from either focal vasculitic infarcts (presumably absent in Ms. C) or antineuronal antibodies producing diffuse brain dysfunction (6).

Treating psychopathology in patients with multiple sclerosis and systemic lupus erythematosus is difficult. Corticosteroids may help or harm. As far as we know, there are no prospective studies of the use of psychotropics in either disorder. Anecdotal reports (summarized in references 3 and 4) describe the usefulness of a variety of medications and ECT. In both illnesses, however, the neurological side effects of standard psychotropics may cause problems (3). In lupus, renal disease may contraindicate the use of lithium.

Anticonvulsants would be an appealing alternative for these patients. To our knowledge, there has been only one previous report of the use of an anticonvulsant, clonazepam, for systemic lupus erythematosus (7) and no reports of its use for multiple sclerosis. Relevant to this issue are reports of the use of carbamazepine for other nonepileptic organic mental syndromes, e.g., bipolar illness secondary to hemispherectomy (8) and psychiatric symptoms in frontal lobe disease (9).

The mechanism of action of valproate in epilepsy and psychiatric disorders is thought to be the potentiation of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter (1). None of our patients had seizures; we speculate that GABA activity important to normal mood and cognition was nonspecifically interrupted because of scattered anatomic lesions in the multiple sclerosis patients and diffuse dysfunction in the lupus patient. Carbamazepine, which also affects GABA activity (1), may treat organic brain syndromes through a similar mechanism. ECT, reportedly effective for psychiatric symptoms in both multiple sclerosis and lupus (3, 4), is also postulated to induce GABA activity (10).

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Occult Thyroid Dysfunction in Patients With Refractory Depression

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Assessment of metabolic rate was useful in evaluating refractory depression in six of 15 women. Five of the six had normal levels of T_3 and T_4; however, each had an elevated thyrotropin-stimulating hormone level or a low metabolic rate. The depressions responded to medication with thyroid hormone.

(Am J Psychiatry 1988; 145:1012–1014)

Although overt hypothyroidism is rarely found in patients with depression, evidence of occult thyroid dysfunction may be present in 25% of depressed patients (1). This evidence includes abnormal response to the thyrotropin-releasing hormone (TRH) stimulation test (2), high titers of antimicrosomal thyroid and antithyroglobulin antibodies (3), and an elevated level of thyrotropin-stimulating hormone (TSH) (4).

Theoretically, when circulating levels of thyroid hormone (T_3 and T_4) are normal, the patient is clinically euthyroid, and "occult" thyroid disease should have no bearing on clinical status. It is conceivable, however, that certain depressed patients have an abnormal tissue response to T_3 and T_4. Direct measures of cellular response would be useful, but thyroid receptor binding assays are not reliable.

One largely discarded method of assessing tissue response is to measure the metabolic rate. This method suffers from a number of limitations and is influenced by a variety of artifacts, but it is the best index of thyroid hormone's metabolic effect (5). Interestingly, most artifacts elevate rather than depress measurements of metabolic rate.

Clinically, we observed that depressed patients with occult thyroid dysfunction were usually overweight, sluggish, bothered by obsessional ruminations, and experiencing cognitive slowing. We performed thyroid studies of 15 consecutive patients referred for refractory depression who had these clinical features.

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METHOD

Fifteen women, ages 24–59 years, whose depression had not responded to outpatient pharmacologic management were studied. The patients were instructed not to eat or drink after midnight on the night before the test and not to smoke or physically exert themselves on the morning of the test.

At the laboratory, the patients were reassured about the test. Blood was obtained for measurement of T_3 resin uptake, T_4 by radioimmunoassay, free T_4, TSH, and antimicrosomal and antithyroglobulin titers. Each subject was put to bed in a quiet, temperature-controlled room for 30 minutes. Then the subject's head was placed in a clear plastic head canopy. The canopy uses an open circuit method in which the patient inhales atmospheric air and the exhaled gases are analyzed for oxygen consumption and CO_2 production. Patients are monitored for 30 minutes; measures are taken only after a steady state is achieved.

Heat production per day was then calculated using the oxygen consumption and CO_2 production data. Body surface area was calculated according to the following formula: body surface area (cm^2)=0.425× weight (kg)×0.725×height (cm). These data were compared to adult standards reported by Aub and DuBois (6) and expressed as plus or minus a percentage deviation from normal basal metabolic rates. Deviations from normal of more than 10% have been used to make diagnoses of hypothyroidism and hyperthyroidism (7).

Results of all tests were reported to the referring psychiatrists, who made final treatment decisions and provided follow-up care.

RESULTS

The results are summarized in table 1. Seven subjects (patients 7–10 and 13–15) had no evidence of occult hypothyroidism. All seven had metabolic rates in the normal or hypermetabolic range. Five of these patients

TABLE 1. Initial Thyroid Measures and Response to Thyroid Supplement of 15 Female Patients With Refractory Depression

Patient	Free T_4 Index (units)[a]	TSH Level (mIU/liter)[b]	Metabolic Rate[c]	Response to Thyroid Supplement
1	2.00	2.8	−13.0	Good
2	2.36	9.1	0.0	Good
3	3.43	6.7	−7.7	Good
4	2.64	9.3	−9.2	Good
5	5.40	0.7	−8.5	Good
6	—	—	−17.0	Unknown
7	2.83	1.6	13.8	Poor
8	4.46	<0.8	4.8	Poor
9	5.48	—	20.1	Supplement not given
10	3.42	1.2	12.2	Supplement not given
11	2.55	8.9	32.3	Fair
12	2.50	5.4	1.7	Unknown
13	2.11	4.7	18.0	Supplement not given
14	1.39	1.6	18.2	Supplement not given
15	2.67	0.4	23.6	Supplement not given

[a]Normal range: 1.10–4.40 units.
[b]Normal value: <4.9 mIU/liter.
[c]Percent deviation from normal.

had normal serum thyroid values, and two had mildly elevated free T_4.

Of the remaining eight patients, one (patient 12) had an elevated TSH level and a normal metabolic rate. This patient was lost to follow-up. Another subject (patient 11) had an elevated TSH level but was hypermetabolic; this patient was given liothyronine, which reduced her TSH level to normal but resulted in only modest clinical improvement.

The remaining six patients showed evidence of occult hypothyroidism and responded clinically to thyroid supplements. The depression of patient 1 had been refractory to several tricyclic antidepressants, monoamine oxidase inhibitors, lithium, and ECT. Because of her low metabolic rate, she was placed on a regimen of tranylcypromine and liothyronine, and excellent clinical results were achieved.

Patient 2, who had a chronic depression, was treated with thyroxine; she became more depressed when her dose of thyroxine was decreased from 200 to 100 μg/day, although the results of her thyroid function tests were normal. After not taking any medications for one month, she had a TSH level of 9.1, although the other values were normal. Thyroxine, 200 μg/day, was restarted, along with imipramine, with good clinical response.

In the case of patient 3, an elevated TSH level and a metabolic rate of −7.7% prompted her psychiatrist to prescribe thyroxine, which successfully relieved her depression.

For patient 4, who had a long history of bipolar disorder, thyroxine, 163 μg/day, had been started because of her elevated TSH level. One year later, the patient developed a major depression. Her TSH level was still elevated, her metabolic rate was −9.2%, and her antithyroglobulin antibody titer was markedly elevated. When the thyroxine was increased to 175 μg/day, she showed marked clinical improvement and her TSH level returned to normal. An endocrinological consultation resulted in a subsequent diagnosis of Hashimoto's disease.

Patient 5 had an elevated TSH level and a benign thyroid nodule. With a dose of 150 μg/day of thyroxine, her depression resolved, the thyroid nodule decreased in size, and her TSH level became normal. However, because she had an elevated serum T_4 level, her doctor lowered her dose of thyroxine to 125 μg/day. Her depression subsequently returned. She improved on a regimen of desipramine and an increased dose of thyroxine (175 μg/day). However, concern that she had iatrogenic hyperthyroidism led to metabolic testing. Because there was no evidence that she was hypermetabolic, her dose of thyroxine was maintained.

For patient 6, the referring doctor wished to increase the dose of thyroxine but was also concerned about provoking iatrogenic hyperthyroidism. Metabolic testing revealed a low metabolic rate, so her dose of thyroxine was raised to 250 μg/day, and she was given dextroamphetamine, up to 40 mg/day. Repeat metabolic testing showed a metabolic rate of −5%, but the patient was lost to follow-up.

DISCUSSION

The clinical suspicion of thyroid dysfunction was borne out in six of 15 depressed patients. Although these six cases were not systematically obtained and represent a variety of clinical scenarios, they all illustrate one common point: monitoring levels of circulating T_3 and T_4 has little usefulness in the clinical management of patients with refractory depression.

In patients 1, 3, and 4, low metabolic rate, in spite of normal levels of circulating T_3 and T_4, prompted addition of or increase in thyroid medication, which resulted in subsequent clinical improvement. The metabolic rates were not extremely low, but taken in the context of elevated TSH levels and clinical response to thyroid hormone, they appear to have been clinically significant.

In patients 5 and 6, a low metabolic rate reassured the physicians that the doses of thyroxine could be safely administered. In patient 2, an elevated TSH level, with normal levels of T_3 and T_4, prompted an increase in thyroid medication which resulted in clinical remission. The case of patient 4 also demonstrates how very small changes in the dose of thyroid hormone can have a major impact on both clinical status and laboratory indices.

Because this was an open study, we made no attempt

to control for medication and only rudimentary attempts to control diet and physical exertion. Nevertheless, it is clear that these patients suffered from some form of occult thyroid disease, perhaps involving blunted tissue response to circulating thyroid hormone. It is interesting that the existence of a group of patients with clinically mild hypothyroidism and elevated TSH levels but normal levels of circulating T_3 and T_4 has been noted in the medical literature (8).

We suggest that for patients with refractory depression who have clinical signs of hypothyroidism, assessments of TSH level, antithyroid antibody titers, and metabolic rate are useful. On the basis of the results of these tests, some patients will benefit clinically from thyroid medication. We intend to test these ideas with more systematic study of a larger sample of patients.

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Serotonergic and Noradrenergic Sensitivity in Obsessive-Compulsive Disorder: Behavioral Findings

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Six of eight patients with obsessive-compulsive disorder had an exacerbation of symptoms when given m-*chlorophenylpiperazine. Fenfluramine and placebo produced mild improvement. Six patients given intravenous clonidine experienced marked reduction in obsessions. Implications for serotonergic and noradrenergic hypotheses of obsessive-compulsive disorder are discussed.*

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Recent findings that obsessive-compulsive disorder is far more common than previously believed and that it responds to antidepressants with potent effects on serotonin (5-HT) reuptake blockade have generated interest in neurochemical models of this disorder. Pharmacological evidence for abnormalities in serotonergic function in obsessive-compulsive disorder stems from the clinical improvement brought about by agents that manifest potent 5-HT reuptake blockade, such as clomipramine, fluoxetine, and fluvoxamine. Furthermore, patients with high pretreatment levels of CSF 5-hydroxyindoleacetic acid (5-HIAA), a 5-HT metabolite, were found to be more likely to respond to clomipramine, and the degree of decrease in CSF 5-HIAA during clomipramine treatment was correlated with clinical improvement (1). Peripheral measures of serotonergic function such as platelet 5-HT levels have also been found to be elevated at baseline in clomipramine responders, and the degree of decrease in platelet 5-HT levels with clomipramine treatment corresponds to the degree of improvement (2).

These findings support a role for 5-HT in obsessive-compulsive disorder and have generated interest in the use of specific pharmacologic probes to further clarify the role of serotonergic function in the disorder. Previous studies with *m*-chlorophenylpiperazine (*m*CPP), a selective 5-HT receptor agonist, have yielded mixed results. Studies with intravenous *m*CPP did not show consistent behavioral results in patients with obsessive-compulsive disorder (3), while studies with oral *m*CPP documented exacerbation of obsessive-compulsive symptoms (4).

The role of presynaptic serotonergic function in obsessive-compulsive disorder is unclear. Studies with fenfluramine, a presynaptic 5-HT releasing agent (marketed as a diet pill), would help to clarify the effects of presynaptic 5-HT augmentation.

Although there are fewer data supporting a role for norepinephrine in obsessive-compulsive disorder, there are some clues to support further investigation of noradrenergic function in this disorder. Some antidepressants with strong effects on 5-HT reuptake blockade fail to relieve obsessive-compulsive symptoms. While clomipramine is a selective 5-HT reuptake blocker, its principal metabolite, desmethylclomipramine, is a potent norepinephrine reuptake blocker. Previous studies in which intravenous clonidine, an α_2 agonist, was used have documented a blunted growth hormone response in a small group of patients with obsessive-compulsive disorder, suggesting down-regulated α_2 receptors (5). There are also case reports of improvement of obsessive-compulsive symptoms after oral doses of clonidine in patients with obsessive-compulsive disorder (6) and in patients with Tourette's disorder (7). We chose to use intravenous clonidine to assess α_2 receptor function in obsessive-compulsive disorder and its role in the production of the symptoms of the disorder.

METHOD

The subjects of the study were eight adult male outpatients who met the *DSM-III-R* criteria for obsessive-compulsive disorder. Their ages ranged from 19 to 46 years (mean=36.8 years), and the duration of illness ranged from 2 years to 31 years (mean=14.8 years). None of the patients had coexistent major affective, anxiety, other psychiatric, or medical disorders. All

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patients signed consent forms after being informed of the possible risks and benefits of the procedures.

All of the eight subjects were given oral doses of *m*CPP, seven of them were given oral doses of fenfluramine, and six of them were given clonidine infusions. Each procedure appeared identical to both the patient and the clinical rater of the patient's symptoms. To maintain the blind conditions, subjects received three capsules by mouth and a slow intravenous infusion of 10 cc of fluid during each procedure. The procedures were separated by at least 48 hours. The order in which the drugs and placebo were given was unknown to both the patient and the clinical rater.

A single dose of the challenge medications was administered. The *m*CPP (0.5 mg/kg p.o.), clonidine (2 μg/kg, by slow intravenous push), and placebo were randomly assigned by a computer-generated balanced design. Fenfluramine (60 mg p.o.), which has a longer carry-over effect, was always administered as the last procedure.

The clinical rater, blind to the medication procedures, used the Clinician Challenge Obsessive-Compulsive Disorder Rating Scale to rate obsessive and compulsive symptoms. This instrument assesses global obsessions and compulsions on a scale from 0 (none) to 4 (severe). These severity ratings were made 30 minutes before each procedure, at the time the drug was administered, and 60, 120, 180, and 240 minutes after the drug was given. Patients' self-ratings and a clinical narrative of each procedure were also recorded.

Pearson correlation matrices were used to correlate changes in the peak severity of obsessive-compulsive symptoms following *m*CPP and fenfluramine with the respective changes in peak blood levels of *m*CPP and fenfluramine.

RESULTS

m*CPP*

Six of the eight patients who received *m*CPP had an exacerbation of obsessions and compulsions beginning 60 minutes after the oral dose was given and peaking 120 minutes afterward. There was a dramatic rise from baseline scores in the obsessive-compulsive disorder severity scores following *m*CPP, in marked contrast to a decrease in these severity scores following the placebo challenge in the same subjects. There was a 123% increase in obsessive-compulsive symptoms over baseline following *m*CPP, in contrast to a 33.5% decrease in these symptoms following placebo challenge. While six of eight patients had an exacerbation of obsessive-compulsive symptoms after taking *m*CPP, none of the patients got worse and four of them got better after receiving the placebo.

Other effects of the *m*CPP included mild anxiety, mild mood changes, and mild nausea or stomach cramps in some patients. In addition, two patients experienced a throbbing headache at the end of the *m*CPP procedure.

The time course for the changes in blood levels of *m*CPP closely paralleled the time course for behavioral exacerbation following the drug challenge. Increase in the severity of obsessive-compulsive symptoms following *m*CPP was significantly correlated with increases in peak *m*CPP blood levels ($r=0.87$, $N=6$, $p=0.01$).

Clonidine

All of the six patients who received clonidine showed a marked reduction in obsessive-compulsive symptoms; the effect peaked 60 minutes after the intravenous dose of clonidine was received. There was a dramatic decrease (81.8%) in the severity of obsessive-compulsive symptoms following clonidine, compared to a mild diminution (33.5%) following placebo. While all six patients who received clonidine had dramatic improvement in their symptoms, four of them had minimal improvement following placebo challenge. Thus, there was evidence of greater diminution of symptoms after clonidine infusion than after placebo. Side effects of the clonidine included hypotension, increased drowsiness, and a feeling of calm.

Fenfluramine

Five of the seven patients who received fenfluramine experienced some improvement in the severity of their obsessive-compulsive symptoms beginning 60 minutes after the oral dose was taken and continuing to 240 minutes afterward. There was a small decrease (35.5%) in symptom severity scores following fenfluramine, which closely paralleled the 33.5% decrease following placebo. Five of the seven patients minimally improved after taking fenfluramine, and four of these seven showed minimal improvement after placebo challenge. The decrease in obsessive-compulsive symptoms following fenfluramine paralleled the decrease in these symptoms during the placebo challenge.

The side effects of the fenfluramine included a feeling of body coolness, mild stomach ache, and mild improvement in mood and decrease in anxiety in some patients.

There were slower and larger increases in blood levels of fenfluramine and norfenfluramine (the principal fenfluramine metabolite) than in blood levels of *m*CPP following the challenges. The peak blood levels of fenfluramine did not correlate with changes in severity of symptoms following fenfluramine ($r=-0.001$, $N=7$, $p=0.49$).

DISCUSSION

It is particularly interesting that obsessions and compulsions can be altered by pharmacological manipulation of serotonergic and noradrenergic function. We found that *m*CPP, a selective 5-HT receptor agonist,

increased obsessions and compulsions in patients with obsessive-compulsive disorder. However, the effects of the presynaptic 5-HT releaser fenfluramine did not significantly differ from those of a placebo; both caused mild improvement in obsessive-compulsive symptoms. This does not appear to be a nonspecific anxiogenic effect of *m*CPP, since patients with obsessive-compulsive disorder do not experience exacerbations of symptoms when given the panicogens sodium lactate (8), yohimbine, and caffeine. Furthermore, the pharmacokinetic effect of *m*CPP, manifested by the significant correlation between peak blood levels of *m*CPP and increased severity of obsessive-compulsive symptoms in individual patients, is important in showing a high specificity.

An exacerbation of obsessive-compulsive symptoms after *m*CPP is consistent with serotonergic hypersensitivity in obsessive-compulsive disorder. There are also anecdotal reports of initial worsening of symptoms following large acute doses of clomipramine or fluoxetine followed by tryptophan. Chronic clomipramine treatment was shown to block the exacerbation of obsessions and the hyperthermic response following oral doses of *m*CPP that had been demonstrated at baseline in a previous study (9). This suggests that down-regulation of 5-HT receptors may mediate clomipramine's antiobsessional effects.

However, fenfluramine does not exacerbate obsessive-compulsive symptoms. One possible explanation for the disparate behavioral results with *m*CPP and fenfluramine is the specificity of these agents. While *m*CPP is a selective 5-HT_{1B} agonist, fenfluramine is a nonselective 5-HT releaser and reuptake blocker that affects various 5-HT receptor subtypes. There is some evidence that 5-HT_{1A} and 5-HT_2 receptors may mediate anxiolytic effects, while 5-HT_{1B} receptors mediate anxiogenic effects (10); this could account for the different behavioral effects seen with these agents.

We found a rapid improvement in obsessive-compulsive symptoms with intravenous clonidine, which suggests that stimulation of α_2 receptors may mediate symptom improvement. However, we also noted that patients were sedated, drowsy, and calm following intravenous clonidine. While the possibility remains that improvement in obsessive-compulsive symptoms is the result of a nonspecific sedating effect of clonidine, other sedatives have not been reported to relieve these symptoms.

It is likely that both serotonergic and noradrenergic systems are involved in obsessive-compulsive disorder. Perhaps the serotonergic system is involved in the lack of certainty and overestimation of possible harm that may be pathognomonic of the disorder, and the noradrenergic system modulates the accompanying anxiety.

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Creatine Kinase Elevation After Neuroleptic Treatment

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Two cases of asymptomatic elevation of creatine kinase levels after oral neuroleptic treatment are described. One patient was successfully challenged with a different neuroleptic. The authors discuss possible reasons for creatine kinase elevation.

(Am J Psychiatry 1988; 145:1018–1019)

While an elevated serum creatine kinase level has frequently been observed in acute psychotic states (1), it most commonly results from intramuscular injections, use of restraints, or other intense isometric activity (2), such as dystonic reactions (3). It has rarely been suggested as a complication of neuroleptic treatment (4), except in neuroleptic malignant syndrome (5). A case of extreme creatine kinase elevation after oral administration of molindone, with only slight evidence of rigidity or other symptoms of neuroleptic malignant syndrome, was recently reported (6). We present two cases of asymptomatic creatine kinase elevation detected by routine screening. About 300 patients per year receive neuroleptics at our facility, all of whom have creatine kinase determinations as part of the SMA-12 autoanalyzer procedure. Attention was directed to the possible role of neuroleptics when the most common causes of creatine kinase elevation had been excluded.

CASE REPORTS

Case 1. Mr. A, a 30-year-old black man with a diagnosis of paranoid schizophrenia, was admitted after becoming agitated and expressing vague homicidal ideation. He had received haloperidol and fluphenazine at other institutions for two similar episodes without complications, but his creatine kinase level had not been measured. The level at admission, after a single intramuscular dose of 5 mg of haloperidol, was 243 mU/ml (normal, <200). He was treated with haloperidol, 15 mg/day p.o., and after 3 days his creatine kinase level was 1765 mU/ml. He showed no evidence of dystonia, rigidity, fever, autonomic lability, change in level of consciousness, or motor hyperactivity and had received no more intramuscular injections. Haloperidol was discontinued, and over the next 3 days his creatine kinase level fell from 1805 to 767 mU/ml. Because of his increasing agitation and hypervigilance, Mr. A was then treated with thioridazine, 300 mg/day p.o. After 2 days his creatine kinase level rose to 1440 mU/ml again with no symptoms of neuroleptic malignant syndrome, use of restraint, or intense isometric activity. Thioridazine was discontinued. The creatine kinase level peaked at 2560 mU/ml and gradually fell to 220 during the next 2 weeks.

Fractionation of the specimens with elevated creatine kinase showed 100% MM band. Mr. A's SGOT and LDH levels were never elevated, but his aldolase level was not determined. His urine was not examined for myoglobin, but there was a transient rise in his serum creatinine level. Mr. A's behavior was subsequently managed successfully with diazepam and clonidine.

Case 2. Mr. B, a 28-year-old white man with a diagnosis of borderline personality disorder, had received haloperidol, perphenazine, and chlorpromazine on other occasions without incident, but his creatine kinase level had not been determined. About 1 month before admission, haloperidol (10 mg/day) had been prescribed. After 2 days Mr. B's creatine kinase level was 253 mU/ml, but it was not further investigated, and haloperidol was discontinued the next day.

During his hospitalization, Mr. B had command auditory hallucinations and was given perphenazine, 4–12 mg/day for 6 days and then 12 mg/day. Mr. B's creatine kinase level rose from 61 mU/ml at admission to 1560 mU/ml on day 9 of treatment. He showed no evidence of dystonia, motor hyperactivity, neuroleptic malignant syndrome symptoms, or self-mutilation. He had neither been restrained nor received injections, but he had lifted weights on one occasion. Perphenazine was discontinued. Mr. B's creatine kinase level peaked at 5580 mU/ml and gradually fell to normal by day 22.

Fractionation showed 100% MM band. The urine showed no myoglobin, and the serum creatinine, SGOT, and LDH levels remained normal. Aldolase was not measured. Four days after discontinuation of perphenazine, the auditory hallucinations recurred and were treated with thiothixene, 10 mg/day. Mr. B's creatine kinase level remained normal during the 18 days of treatment and after a subsequent weightlifting session.

DISCUSSION

The close connection with neuroleptic administration and the absence of dystonia, motor hyperactivity, symptoms of neuroleptic malignant syndrome, and other causes of rhabdomyolysis (2) suggested that the

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elevated creatine kinase levels in these cases resulted from the drugs. The successful challenge in case 2 indicated intermittent or agent-specific vulnerability, as in neuroleptic malignant syndrome. These proposals must be qualified by the fact that, in the studies reviewed by Meltzer (1), similar patterns of rise and fall of creatine kinase were frequently observed in psychotic patients who had not received neuroleptics. Creatine kinase elevations usually occurred near the onset of the psychotic episodes or during symptom exacerbations later in the hospitalizations. Such elevations were rare in nonpsychotic patients except in association with the previously mentioned factors (2). Mr. A, however, was not actively psychotic during this hospitalization, which is consistent with his successful management without antipsychotic medication. Mr. B had two brief psychotic episodes, but creatine kinase elevation occurred during only one of them. It is also intriguing that in about 20% of the psychotic patients with creatine kinase elevations in the studies reviewed by Meltzer (1), the elevation was first noted during oral neuroleptic treatment.

While the precise source of the creatine kinase elevation is unclear, it is probably a sign of damaged muscle membranes, which could progress to frank rhabdomyolysis (6). The leakage of creatine kinase before leakage of the much smaller myoglobin molecule suggests factors other than membrane porosity (7). These might include inhibition by neuroleptics of calmodulin function, protein kinase C, or other enzymatic processes (8), although the drug concentrations needed to produce such in vitro inhibitory effects have been shown to be micromolar, and only nanomolar levels result from clinical doses of neuroleptics (9).

More vigorous investigation of elevated creatine kinase levels in patients receiving neuroleptics, including muscle biopsies, would clarify the distinction between neuroleptic side effect and subclinical myopathy of psychosis (1). Contracture testing would be helpful in assessing the risk for malignant hyperthermia, as in some cases of neuroleptic malignant syndrome (5).

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Evidence for Atypical Depression in Parkinson's Disease

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The Research Diagnostic Criteria were applied to 16 depressed patients with Parkinson's disease and 20 depressed multiple sclerosis patients. Diagnoses of anxiety and panic disorder were significantly more frequent among the patients with Parkinson's disease. These patients may experience atypical depression.
(Am J Psychiatry 1988; 145:1020–1022)

Several clinical reports (1–4) in recent years have documented a 40%–50% risk for the occurrence of significant depressive symptoms during the course of idiopathic Parkinson's disease. The evidence indicates that the affective disorder is not consistently related to severity of motor disturbance or to duration of neurologic disease, although it may be associated with diminished CSF serotonin turnover (5). Descriptive features of these depressive episodes have generally not been carefully reported. Only Mayeux et al. (3) have presented the results of a standardized psychiatric interview with such patients: the instrument used was the National Institute of Mental Health Diagnostic Interview Schedule. Mayeux et al. described depressed Parkinson's disease patients, who had prominent complaints of sleep disturbance, fatigue, psychomotor retardation, difficulty concentrating, loss of self-esteem, and guilt.

In our studies of affective disturbance among patients with neurologic diseases, we have made the clinical observation that atypical features of panic and anxiety seem to occur commonly among depressed Parkinson's disease patients (6). We have not commonly observed such features among patients with multiple sclerosis, who experience a risk for affective disturbance during the course of the disease in the range of 40%–60% (7–9). As in Parkinson's disease, no definite relationship has been established between duration or severity of neurologic disease and affective symptoms. To test our hypothesis that depressive episodes in Parkinson's disease may be qualitatively distinct from depressive episodes in multiple sclerosis, we performed a comparison study using a standardized psychiatric interview.

METHOD

We reviewed the medical records of the approximately 200 patients with idiopathic Parkinson's disease who are followed in our clinic and selected 26 patients whose records indicated significant recent depressive symptoms. After giving informed consent, these patients were interviewed by a psychiatrist (R.B.S.) using the lifetime version of the Schedule for Affective Disorders and Schizophrenia (SADS-L). Psychiatric diagnoses were made according to the Research Diagnostic Criteria (RDC), and concurrent diagnoses of anxiety and affective disorders were permitted. We selected SADS/RDC psychiatric diagnoses for this study because this diagnostic system permits a diagnosis of generalized anxiety disorder after a relatively brief duration of symptoms (2 weeks). Sixteen patients with Parkinson's disease met the criteria for either major or minor depressive disorder.

The comparison subjects attended the multiple sclerosis clinic at the University of Rochester, in which approximately 350 patients are followed. The subjects in our study were 20 consecutive patients who met the RDC for major depressive disorder during 1984–1986. The data from their interviews were reviewed by the psychiatrist who conducted the SADS-L interviews with the Parkinson's disease patients. The multiple sclerosis patients and interview data have been described previously (9).

The degrees of neurologic disability were quite heterogeneous for both groups; the Hoehn and Yahr disability stages ranged from 1 to 4 for the Parkinson's disease patients, and the Kurtzke Expanded Disability Status Scale scores ranged from 2 to 7 for the multiple sclerosis patients.

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TABLE 1. Clinical Features of Depressed Patients With Parkinson's Disease or Multiple Sclerosis

Patient	Age (years)	Sex	RDC Diagnoses	Age at Onset (years)		
				Neurologic Disease	Depression	Panic/ Anxiety
Parkinson's disease						
1	63	M	Major depression, panic disorder	58	61	61
2[a]	76	F	Minor depression[b], panic disorder	66	54	67
3[a]	58	F	Major depression, panic disorder[b]	48	53	50
4	65	M	Major depression, generalized anxiety[b]	58	63	58
5	57	M	Major depression[b], generalized anxiety[b], panic disorder	51	21	21
6	60	M	Panic disorder[b], generalized anxiety[b], minor depression[b]	50	54	54
7	56	F	Major depression[b], generalized anxiety	54	52	52
8	69	M	Major depression[b], paranoid psychosis	52	64	
9	66	F	Major depression[b], generalized anxiety[b]	56	64	64
10[a]	52	F	Major depression[b], panic disorder[b]	46	30	47
11	54	M	Minor depression[b]	49	49	
12[a]	64	F	Minor depression[b], panic disorder[b]	63	62	63
13	72	M	Minor depression[b]	70	70	
14	64	F	Major depression, paranoid psychosis[b]	57	60	
15	75	F	Minor depression[b], panic disorder[b]	65	72	72
16	70	M	Minor depression[b], generalized anxiety[b]	55	69	68
Multiple sclerosis						
1	46	F	Major depression[b]	20	40	
2	22	F	Major depression[b]	17	21	
3	49	F	Major depression[b]	39	41	
4	45	M	Major depression[b]	30	42	
5	30	F	Major depression[b]	21	29	
6	36	F	Major depression[b]	32	35	
7	44	F	Major depression[b]	43	43	
8	55	F	Major depression[b], conversion disorders	50	55	
9	34	F	Major depression[b]	29	33	
10	25	F	Major depression[b]	16	24	
11	38	F	Major depression[b]	33	23	
12	27	F	Major depression[b]	25	18	
13	33	F	Major depression[b]	20	30	
14	25	F	Major depression[b]	22	24	
15	35	F	Major depression[b]	30	33	
16	33	M	Major depression[b], drug abuse	24	32	
17	39	F	Major depression[b]	16	22	
18	22	F	Major depression[b], atypical psychosis	16	21	
19	37	F	Major depression[b], generalized anxiety	24	30	Lifelong
20	51	F	Major depression[b], panic disorder	49	15	15

[a]History of mild generalized anxiety throughout adult life.
[b]Current disorder.

RESULTS

The RDC diagnoses and ages at onset of neurologic and psychiatric disorders for the two samples are shown in table 1. Twelve of the 16 depressed Parkinson's disease patients met the criteria for past or present generalized anxiety disorder or panic disorder, while only two of the depressed multiple sclerosis patients met these criteria ($\chi^2=13.2$, df=1, $p=0.0003$ with Yates' correction). Eight (50%) of the Parkinson's disease group and 18 (90%) of the multiple sclerosis group were women, a difference which is also statistically significant ($\chi^2=5.2$, df=1, $p<0.02$ with Yates' correction). In seven of the eight Parkinson's disease patients with panic disorder, the clinical onset of panic occurred after the onset of neurologic symptoms and the initiation of therapy with dopamine agonist medication. In four of these patients (patients 3, 6, 15, 16) there was a temporal relationship between motor on/off phenomena and the panic attacks. Three patients tended to experience panic attacks during off periods, and one experienced them during periods of peak dose dyskinesia. All Parkinson's disease patients were taking dopamine agonists at the time of interview. None of the affective or anxiety diagnoses among the multiple sclerosis patients was made during a period of corticosteroid therapy.

DISCUSSION

These preliminary clinical observations suggest that depression frequently coexists with panic or anxiety in Parkinson's disease and that this affective disorder may be qualitatively different from that seen in multiple sclerosis. The relatively late onset of panic and anxiety among the patients with Parkinson's disease suggests a pathophysiologic relation between the neurologic disease or its treatment with dopamine agonists and the psychiatric symptoms. A possible relationship between panic or anxiety and falling levels of CNS dopamine is suggested by the three patients who experienced panic attacks consistently during off periods. Confirmatory studies are needed, however, since in this report only the investigators who interviewed the multiple sclerosis patients and made their diagnoses were blind to the hypothesis being tested.

If confirmed, such an observation might be of considerable heuristic importance. There is evidence that metabolic alterations of CNS norepinephrine and dopamine transmission may be associated with anxiety disorders (10). Both locus ceruleus noradrenergic and ventral tegmental dopaminergic neurons are known to degenerate in idiopathic Parkinson's disease. In addition, dopamine agonist therapies induce cyclical alterations of central catecholamine metabolism, which may be involved in the generation of panic and anxiety. The affective disturbance of Parkinson's disease may provide us with a neurologic model for one of the atypical depressions.

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DSM-III Axis I Diagnoses of Indian Psychiatric Patients With Somatic Symptoms

Shekhar Saxena, M.D., Mahendra K. Nepal, M.D., and Devinder Mohan, M.D.

When DSM-III *criteria were applied to 123 Indian psychiatric outpatients with predominantly somatic symptoms, the most common axis I diagnoses were dysthymic disorder (36.6%) and generalized anxiety disorder (11.4%). Thirty-nine percent of the patients fitted only into atypical diagnostic categories.*
(Am J Psychiatry 1988; 145:1023–1024)

A significant proportion of all patients attending psychiatric clinics in developing countries have predominant somatic symptoms without any causative physical disease. Sociocultural, educational, and racial factors may be responsible for this phenomenon of somatization (1–3). Diagnostic classification of patients with predominantly somatic symptoms is an important area of psychiatric research, especially for the developing countries (4). The creation of a separate category of somatoform disorders in *DSM-III* was a major advance in this area. However, we are unaware of any published work on the application of *DSM-III* criteria to patients presenting with somatic symptoms. In this paper we report on the *DSM-III* axis I diagnostic categories assigned to such patients at a psychiatric clinic in India and comment on some of the difficulties we encountered during this classificatory exercise.

METHOD

We conducted a prospective study of adult outpatients attending the psychiatric clinic of a hospital in New Delhi. Initially, 150 consecutive patients who had two or more somatic complaints were chosen for study. Patients with psychotic disorders, including major affective disorders, or any physical disease capable of producing the somatic symptoms were then excluded, leaving 123 patients in the study. A detailed psychiatric assessment was done according to the guidelines provided by MacKinnon (5). Diagnoses on *DSM-III* axis I were made jointly by a resident (M.K.N.) and a consultant (S.S.), who followed exactly the *DSM-III* criteria. These two clinicians were fully conversant with *DSM-III* and were using it extensively in patient care as well as in other research activities. However, they were not blind to the objectives of the study.

Of the 123 patients, 78 (63.4%) were male and 45 (36.6%) were female. Most (N=93, 75.6%) were young adults (16–35 years of age) and most (N=104, 84.6%) were Hindus; 72.4% (N=89) were married, and 78.0% (N=96) had had at least 11 years of schooling. They were a heterogeneous group with respect to occupation, but about 25% were salaried employees and about 25% were housewives.

RESULTS

The mean±SD number of complaints presented by the patients was 6.8±3.3. Of these, 6.0±2.9 were somatic in nature. The most frequent somatic complaints were aches and pains in the head, abdomen, legs, back, chest, neck, and shoulders. Other common symptoms were sleep and appetite disturbances, weakness, giddiness, distention of the abdomen, palpitations, constipation, a sensation of heat in the body, and a choking sensation. The most frequent psychological complaints were sadness, lack of interest, and a feeling of nervousness and tension.

The distribution of *DSM-III* axis I diagnoses for the patient is given in table 1. The most frequent diagnoses were dysthymic disorder and generalized anxiety disorder. Forty-eight patients (39.0%) could not be assigned any specific axis I diagnosis. These patients were assigned residual, atypical diagnoses (atypical somatoform disorder, atypical depression, and atypical anxiety disorder).

DISCUSSION

It is not surprising that the most common diagnoses were dysthymic and generalized anxiety disorders in view of earlier findings that patients with depression and anxiety frequently complain of somatic symptoms

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TABLE 1. *DSM-III* Axis I Diagnoses of 123 Indian Psychiatric Outpatients

Diagnosis	N	%
Dysthymic disorder	45	36.6
Generalized anxiety disorder	14	11.4
Hypochondriasis	6	4.9
Psychogenic pain disorder	5	4.1
Somatization disorder	2	1.6
Panic disorder	1	0.8
Conversion disorder	1	0.8
Inhibited sexual excitement	1	0.8
Residual, atypical categories	48	39.0

(1, 6); this is especially true of patients in developing countries (7). The total percentage of patients whose diagnoses were in the various subcategories of somatoform disorder was 11.4%, out of which only 1.6% were given a diagnosis of somatization disorder. A low prevalence of somatization disorder has also been reported in the community (8) and in a clinic sample with diagnoses of hysteria (9).

One of the important findings of this study was that 39.0% of all the psychiatric patients presenting with predominantly somatic symptoms could fit only into the residual, atypical categories of *DSM-III* axis I diagnoses. There are several reasons for this. 1) We were not always able to document the presence of the psychosocial stressors and psychogenic factors required by *DSM-III* for the diagnoses of adjustment disorder, psychogenic pain disorder, and conversion disorder. 2) Our patients did not always fulfill the criteria of several years' duration and presence of at least 14 symptoms for women and 12 for men required for the diagnosis of somatization disorder. For many patients, the duration was shorter and the symptoms fewer in number. 3) Some patients did not meet the requirement of a minimum total duration of 2 years for the diagnosis of dysthymic disorder. This left no specific category for nonmajor, fluctuating depression of less than 2 years' duration that was not induced by stress.

The provision of undifferentiated somatoform disorder (300.70) in *DSM-III-R* and undifferentiated somatization disorder (F-45.1) in the draft of *ICD-10* is a positive development; many of our "atypical" patients would have fitted into these categories. The clinical and psychosocial characteristics of patients in these undifferentiated and atypical subcategories require further study.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

PSYCHIATRY AND ANTIPSYCHIATRY

The Reality of Mental Illness, *by Martin Roth and Jerome Kroll. Cambridge, Cambridge University Press, 1986, 128 pp., $39.50; $12.95 (paper).*

Martin Roth and Jerome Kroll have written a very well-reasoned rebuttal to the antipsychiatrists. The title itself is similar to Szasz's *The Myth of Mental Illness* (1). At first glance it seems that the need for such an essay has passed. After all, it has been almost 20 years since Szasz, Laing, Foucault, and Basaglia were in vogue. The debate has been settled: mental illness does indeed exist. A funny thing happened as I was preparing this review. Each morning the *New York Times* reported the status of a court case involving the involuntary commitment of a homeless woman who had spent the previous winter living on a street in New York City. She had a history of previous psychiatric hospitalizations and had evidenced bizarre behavior and deteriorating personal hygiene. The city's psychiatrists and her family testified that she was mentally ill and in need of hospital care. The civil liberties lawyers representing the patient convinced the judge that she was not mentally ill but exercising a free choice and that society was not to impose such values. Obviously, the issue is very much alive and has major implications for questions of involuntary hospitalization, refusal of treatment, and the insanity defense.

These authors are well prepared for the task. Sir Martin Roth is an exceptionally distinguished British psychiatrist, probably most familiar to Americans as a coauthor of the text *Clinical Psychiatry* (2). Jerome Kroll has a special interest in psychiatry and the mentally ill in history, especially the Middle Ages. Their respective backgrounds are evident in the blending of clinical, historical, and philosophical perspectives as they discuss the issues.

The volume begins with a review of the positions of the antipsychiatrists. These vary and overlap to a great degree but usually contain a mix of two positions: either mental illness does not exist or, even if it does, it is caused by society's labeling or failing to reduce social and economic stressors. The chapter on psychiatric disorders in history provides some good vignettes. For example, Isidore of Seville (560–636 A.D.) included mania and melancholia in his catalog of diseases. The thorny mind-body problem, a core question, is well treated. (We all know Descartes caused it all.) The authors do not attempt a definitive answer but sensibly point out that the resolution of the question of mental illness does not require the final answer on the mind-body question. The last section addresses involuntary hospitalization and the insanity defense in a cogent and realistic way.

A recent book by Hirsch entitled *Cultural Literacy* (3) has a list of topics with which every literate American should be familiar. Hirsch makes the point that in order to assimilate new information we need cognitive schemata in which to process the new information—a frame of reference. Roth and Kroll demonstrate "psychiatric literacy," a familiarity with the history and philosophy as well as the medicine and psychiatry required to deal with such questions as involuntary hospitalization and the insanity defense. There are no easy answers. These issues often involve questions of competing values, of the individual and society, of freedom of choice, and of the right to treatment. Such questions have been faced by every major civilization and taken up by all the major religions and philosophies. Any simplistic solution with an overemphasis on a single value to the exclusion of others will be wanting. "Psychiatric literacy" may prevent some of the pitfalls.

I recommend *The Reality of Mental Illness.* Psychiatrists will find it interesting, and it would be a very useful gift to our friends in the law.

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Witchdoctors and Psychiatrists: The Common Roots of Psychotherapy and Its Future, *revised edition of The Mind Game (1972), by E. Fuller Torrey, M.D. New York, Harper & Row, 1986, 308 pp., $8.95 (paper).*

In 1972, Fuller Torrey, fresh from his psychiatry residency and with a master's degree in anthropology in hand, published *The Mind Game: Witchdoctors and Psychiatrists* (1). That widely read book aimed at deriving a more adequate framework for understanding the activities and outcomes of psychotherapists around the world by comparing folk healers in traditional societies with what Torrey took to be their modern counterparts in the West. In 1986, 14 years later, Harper & Row published this revised edition of *The Mind Game.*

This new edition involves a curious kind of updating. Torrey goes to some pains to include in his review of key works on psychotherapy the latest and most important publications. His selections from the psychotherapy literature are clearly based on broad-ranging and scholarly reading. Yet, for the most part, his review of the cross-cultural literature on traditional healers is terribly out of date. He relies heavily on the same sources canvassed in his first edition; his survey of more recent works is highly selective, very limited, and seems to be based on a lack of knowledge of major developments that have transformed the anthropological study of this subject over the past decade and a half.

The same paradox affects the content of Torrey's chapters. The section on the components of psychotherapy is a thor-

ough review. It is written with verve and commendable conciseness in a popular idiom that is a delight to read and should be accessible to a wide audience of laypersons and professionals unfamiliar with psychotherapy. Torrey, following many students of the subject, takes communication to be the essence of psychotherapy. The key components are the well-known shared world view, personal qualities of the therapist (empathy, warmth, genuineness), expectations of the client (faith, hope, trust, emotional arousal), and the development of a sense of mastery. Nothing very new for an audience of experts. But Torrey's review is aimed at quite another audience. It is, moreover, a simply marvelous read and convincing to boot.

Torrey holds the differing techniques of therapy to be far less important than their shared components in the creation of desired outcomes. His best chapters, to my mind, are those which review the efficacy of psychotherapy. Again the message is familiar: psychotherapy works for a wide range of mental health problems but not for brain disease, and most forms of psychotherapy are effective without evidence of a single element in practice or training that determines success. There are no surprises here; yet there is so much good clinical sense in Torrey's overview and his conclusions are so judicious that the popular style makes these chapters an appealing quick introduction to the subject which can be recommended for neophyte therapists and anyone else interested in what is known and what it all means.

It is when Torrey moves away from psychotherapy per se and tackles the cross-cultural issues that serious problems begin to mount. The last decade of research by medical anthropologists has clarified the remarkable diversity among practitioners of traditional healing systems. In Indian and Chinese cultural settings, for example, there is almost as much intracultural diversity among the wide variety of religious healers; members of literate traditional healing professions (Ayurvedic medicine and traditional Chinese medicine); herbalists; acupuncturists; bone-setters; experts in meditation, massage, and exercise; fortunetellers; pharmacists; and dozens of other types of healers as there is between these healers and practitioners of biomedicine (2, 3). The cross-cultural diffusion of healing systems is simply staggering. Practitioners of Ayurvedic and traditional Chinese medicine practice in North America; homeopaths and naturopaths trained in European indigenous traditions practice in India and Hong Kong. McGuire (4) documented more than 100 distinctive forms of traditional healing practiced by curers in a middle-class suburb of New York City. Research also discloses that the practices of primary care physicians and psychiatrists are substantially shaped by local cultural traditions—i.e., they are "indigenized"—so that internists in rural Thailand, family therapists in India, and psychiatrists in China practice in ways that diverge substantially from the orthodox practices these professions have established in the West (3, 5–7). Thus, when Torrey refers to all nonbiomedical healers in the non-Western world as witchdoctors and makes sweeping generalizations concerning who they are and what they do, more is confused and concealed than is revealed.

Several related problems trouble me as well. Although Torrey shows sympathy for and understanding of the practical problems faced by healers in the Third World, his desire to emphasize the similarities and play down the differences—a widely shared strategy in cross-cultural psychiatry—encourages ethnocentrism. Isn't it time to cease asking in what ways the healers around the world resemble Western psychiatrists and fundamentally reorient the question by asking instead in what ways psychotherapy differs from or resembles the many indigenous healing systems worldwide of which it forms a very small part? That is to say, shouldn't the criteria used to establish differences and similarities in practice be based on important findings from indigenous healing systems, which offer the appropriate empirical data base from which to generalize, rather than on findings from just one particular (albeit diverse), largely Western category of healing system, i.e., psychotherapy? In fact, scholarly reviews of healing (8–10) are increasingly framed in this fashion.

Torrey proposes establishment of local regulations for licensing and standards for practice for all healers. The solution makes sense in the professional sector of mental health care but is naive for folk healing both here and especially abroad. Folk healing by definition is pluralistic, unlicensed, unregulated, and often only quasilegal or even illegal. Regulations and standards for folk healers will be extraordinarily difficult to work out and are likely to have to vary so widely from one local context to another that they will be incomparable. But there are even larger problems that make me wonder if Torrey has had recent experience in a non-Western society. Regulations and standards will require the bureaucratization and professionalization of folk healers. At present, one of their great strengths is that folk healers in the developing world are not organized in modern social institutions and therefore are able to resist Westernization and cooptation by the medical profession. Professionalization may undermine precisely those practices which contribute to the success of folk healing: empathy, trial and error innovation, minimal routinization, integration of secular and religious methods, consonance with local cultural values and idioms, and access for those least oriented to Western professional attitudes. Moreover, there is a serious danger in many societies that the institutional incorporation of folk healers could be organized by unscrupulous professionals as a means of expanding professional services, not in the service of providing more culturally sensitive care but to increase professional income. Indeed, this has happened in several societies. Torrey's suggestion may be appropriate for pastoral counselors and professionals in alternative healing in North America, but it is a poor prescription for the Third World. Here again, cross-cultural differences urge caution.

Torrey's book, then, will be different things for different people. As a popular introduction to the essential issues in psychotherapy it can be enthusiastically recommended to educate laypersons and beginning therapists. It should not be read as a scholarly review of the current status of cross-cultural studies of healing, however. It is to be hoped that in preparing the third edition Dr. Torrey will treat the current anthropological literature with the same degree of seriousness and sagacity that he brings to the literature on psychotherapy. That should result in just the kind of volume which needs to be written and for which he would seem to be an ideal author.

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SEXUALITY

Sexual Intimacy Between Therapists and Patients, *by Kenneth S. Pope and Jacqueline C. Bouhoutsos. New York, Praeger, 1986, 182 pp., $29.95; $14.85 (paper).*

More than 90% of psychiatrists and other mental health professionals, according to available data, do not become sexually involved with their patients because they know such involvement to be unethical, exploitative, and harmful to their patients. Despite these somewhat reassuring statistics, this book should be of interest to all psychiatrists. One cannot practice nowadays without encountering patients who have been sexually exploited by previous therapists or knowing colleagues who may be in danger of or in the midst of such involvements. The issue is important also to those who teach and train younger colleagues or who administer treatment programs. Finally, none of us can claim certain, automatic immunity from the problem.

Pope and Bouhoutsos are well qualified to have written this book. Both have been involved in research, in clinical work, and in professional society programs dealing with patients and therapists who have been sexually intimate, and both have contributed to an otherwise sparse literature on the subject. Their aims are ambitious but they accomplish them remarkably well.

The book is addressed to mental health professionals, patients, and lawyers. Although the authors are unflinching in recognizing the harm done by sexual involvement with patients and clear-eyed in demolishing rationalizations and myths, the book is scholarly and devoid of sensationalism and zealotry in both tone and content. Complexities and conflicting needs are identified and discussed. Respect for patients and their needs, for the process of psychotherapy, and even for the problems, needs, and rights of offending clinicians permeates the book. No easy solutions are promoted.

The book is well organized and not laborious to read. After a chapter outlining some common scenarios for the occurrence of sexual intimacy in treatment and its sequelae, the second chapter identifies and then discusses the legal, ethical, and theoretical aspects of the prohibition against such intimacy and shows why it is always exploitative. An important chapter deals with therapists at risk. Here the data put several misconceptions to rest. Not only young, inexperienced, or poorly trained therapists but, not uncommonly, older, established practitioners—even respected leaders in their fields—get involved. Attention during training to the patient-therapist sex issue had little preventive effect in one national study of social workers, although it is also clear that many therapists have major misconceptions (or rationalizations) for "when therapist-patient sex is OK." The authors wisely suggest that training programs pay more attention to applicants' "personal and professional values"—i.e., character—before admission to psychotherapy training and that far greater attention in supervision needs to be paid to almost universally occurring sexual countertransference feelings and their management. Training programs must also be strict in prohibiting sexual involvement between teachers or supervisors and trainees: therapists who have been sexually involved with their faculty seem significantly more likely to act out sexually with their own trainees and patients later.

Chapter 4 deals with the vulnerabilities of patients to sexual involvement. This chapter, while drawing distinctions, underscores a rather general vulnerability under the influence of transference, particularly for patients undergoing major stresses. The more vulnerable and needy the patients are, the greater is the likely ensuing harm. An important caveat is that patient pathology observed following sexual involvement with a therapist may be caused by such involvement rather than a precursor to it, but the book is perhaps too diffident, possibly out of the desire to avoid "blaming the victim," in identifying the kind of pathology in patients that is conducive to their being victimized.

The chapter on the consequences to patients of a therapist's sexual exploitation describes research and clinical findings that, together with the first chapter and the one on treatment issues, should convince everyone of the profound harm done by such involvement. A specific symptom group, akin to posttraumatic stress syndrome, may be frequent. Relationships are severely disrupted and entire families are often damaged. Additionally, these patients are deprived of appropriate treatment for the problems that originally made them seek treatment, and their trust in all helping professionals is undermined, leading to the vulnerabilities and difficulties in subsequent treatment that the book next examines and addresses in several excellent chapters.

Pope and Bouhoutsos recognize the community's interest in halting the exploitative activities of therapists by several well-explained complaint and legal channels available to patients. They also note the frequent therapeutic benefit to patients of taking such action. They recognize, however, that this is a path to be taken only after much deliberation and preparation, and then not by all patients. They also know that subsequent therapists must give priority to therapy and cannot be advocates as well or be in the position of having to report an offending therapist if it is against the patient's wishes.

Final chapters address the roles of patients, lawyers, and potential expert witnesses. The book ends with checklists for therapists to evaluate their own vulnerability to sexual acting out and, more usefully, for patients to alert them to inappropriate or questionable behavior by therapists that should act as a warning signal.

Once again, the book squarely addresses many myths and misconceptions in making it clear that "the therapist is solely responsible for ensuring that sexual contact with the patient never, under any circumstances, occurs." The wishes or consent of patients, "falling in love," and having terminated treatment are shown to be irrelevant. My summary cannot

do justice to the richness of information and the thoughtfulness of this book, and I urge all psychiatrists to read it.

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The "Sissy Boy Syndrome" and the Development of Homosexuality, *by Richard Green, M.D. New Haven, Yale University Press, 1987, 409 pp., $40.00.*

Psychiatry's retrospective study methods, its failure to appreciate the multiple dimensions of sexual identity (1), and its passionate preoccupation with homosexuality as a disorder have delayed the emergence of a convincing, clinically useful understanding of the origins of male homosexuality. Now, however, previous common-sense, clinical, and research suggestions have been prospectively verified by Richard Green's impressive book, *The "Sissy Boy Syndrome" and the Development of Homosexuality.* As a result of this work, it can be confidently said that persistent preschool femininity is a strong predictor of adolescent and young adult homoeroticism. This relationship was arduously proven in Dr. Green's 15-year study of 66 pervasively feminine and 56 conventionally masculine boys. He comprehensively evaluated these children and their parents during the early 1970s with objective measures and separate and conjoint interviews. Follow-up evaluations ranged from every 18 months to none at all—57 of the feminine boys and their families had at least one follow-up interview; masculine boys had less extensive follow-up.

The early chapters contain erudite literature reviews of the determinants of sex differences in young children and the development of masculinity. Once the distinctions between data-based findings and speculation-based notions are drawn, it becomes clear that no scientist can endorse pronouncements about the development of masculinity except as hypotheses for testing. Despite Dr. Green's marvelously portrayed tension between science and nonscience, it is reassuring to realize that every approach to the psychosocial origins of homosexuality focuses on parent-child relationships and that investigators of all persuasions think that more than biology is involved.

Here are a few condensed findings that discriminated between the control subjects and the feminine boys, who cross-dressed, avoided rough and tumble play, wished to be girls, did not desire to be like their fathers, paid attention to feminine fashions, and showed female doll-play patterns: 1) In the first 5 years of life, parents spent less time with feminine sons than with masculine ones. 2) A strong correlation existed between degree of femininity and parental support for cross-gender behaviors. 3) Mothers of feminine boys had had more distant relationships with their own mothers. 4) Sons became more feminine if their fathers had moved away from the family before the child's 5th birthday. 5) Sexual satisfaction of parents of feminine sons was less than that of parents of masculine sons. 6) Parents of feminine sons thought their sons were more beautiful and feminine than did parents of masculine ones. 7) Feminine boys were lighter in weight and had more hospitalizations at a younger age. Dr. Green follows these and other data-based observations, however, with a caveat about the variability of these patterns in the families of feminine sons.

The most important finding of the study was that three-fourths of the feminine boys became homosexual or bisexual, while only one of the control subjects became bisexual. The continuation of cross-gender behavior at age 12 strongly correlated with subsequent homosexuality. Six of the feminine boys who were heterosexual during adolescence eventually became exclusively homosexual; two, however, consolidated a conventional orientation. The developmental pathways of seven subjects are illustrated in the edited transcripts from interviews during boyhood, adolescence, and young adulthood. The preschoolers demonstrated a great similarity in their feminine patterns, but their gender identity and orientation outcomes showed more diversity. (The third dimension of sexual identity, intention, was not studied.) The family forces that may have generated the early cross-gender behavior were likewise diverse.

The author uses three approaches to explain the origins of femininity and homosexuality. First, he offers identical twins who were discordant for childhood femininity as a clinical metaphor for the understanding of the interaction of genetic and psychosocial influences. Second, he engagingly presents many of the subjects' own views on the question. Third, he presents his synthesis after further discussion of the limitations of the research methodology and the uncertainty of interpreting data-based findings.

Dr. Green's synthesis is humble—doubt abounds. Many forces interact, he admits; children are not temperamentally equal. Some babies have a strong natural attraction to feminine softness and tenderness. Parental attitudes toward the sex of their fetus influence their treatment of their infant. Medical problems can generate a frail child. Families have a system of rewards for gender-role behaviors. Disinclination for rough and tumble play emerges early in life. The boy feels a vital identification gap with his father, the origin of male object hunger of feminine boys to reach back to parents and grandparents. However, when the total variance from these factors is calculated, it does not begin to account for the individual differences among children in how they react and adapt to similar social and psychological circumstances.

Dr. Green is disappointed that the sources of boyhood femininity are not more clear. He knows they derive from a complexity that his model of science cannot elucidate. On the other hand, science has done an admirable job in demonstrating a link between preschool femininity and homoeroticism. (This is not to say that boyhood femininity is the antecedent of all homosexuality.) Dr. Green has shown that this childhood state only rarely becomes late adolescent transsexualism. He has reaffirmed the scientific difficulties in accounting for individual differences and has convincingly illustrated the inability of psychological theories to grasp the interface between the innate and the socially determined. And he has persevered for at least 15 years.

Dr. Green presents a state-of-the-art study in a highly readable style that should be part of the educational requirement of all mental health professionals, not only because of the main topic but also because of its exposition of behavioral science. When something that improves on Dr. Green's science comes along, we shall gravitate to it. Until then, a new standard of erudition and humility is before us.

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PSYCHOANALYSIS

The Development of Psychoanalysis: Classics in Psychoanalysis Monograph 4, *by Sandor Ferenczi and Otto Rank. Madison, Conn., International Universities Press, 1986, 68 pp., $25.00.*

Throughout 1922, tensions were increasing among the members of Freud's famous "Inner Committee," a group that controlled the psychoanalytic movement. Ferenczi and Rank in 1923 completed *The Development of Psychoanalysis*; in the same year Rank's *Trauma of Birth* appeared. The Classics in Psychoanalysis series, edited by George H. Pollock, has reprinted Caroline Newton's English translation of *The Development of Psychoanalysis* as it was originally published in 1925, and in so doing has served the psychiatric and psychoanalytic community well by rescuing it from obscurity.

This little monograph is packed with provocative ideas that will be mainly of interest to those practicing psychoanalytic therapy. Some of these ideas are of current value, but others led Ferenczi and Rank to advocate a confusing hodgepodge of psychoanalysis and suggestion. In retrospect the monograph makes fascinating reading.

The authors downplay the intellectual aspects of explanation and interpretation in psychoanalytic therapy and stress the importance of repeating crucial relationships in the treatment under the influence of the repetition compulsion. At times they advocate an "active" form of intervention on the part of the analyst, even hypnosis or suggestion, in the service, as they see it, of facilitating this repetition. This "active therapy" for the ostensive purpose of facilitating feelings and emotions in the treatment was correctly perceived by their contemporaries as a major divergence from standard psychoanalytic technique, fraught with problems of countertransference acting out.

There are some fascinating comments about narcissistic countertransference contained in the monograph itself that would make good reading for any psychotherapist. For example: "The development of a kind of narcissistic countertransference which provokes the person being analyzed into pushing into the foreground certain things which flatter the analyst and, on the other hand, into suppressing remarks and associations of an unpleasant nature in relation to him" (pp. 41–42). The authors even stress that failures in analysis can be attributed to the narcissism of the patient as a consolation for the analyst, since "it is not difficult to find proofs in his behavior and thoughts for the narcissism of the patient" (p. 42).

The latter part of the monograph discusses the relationship between theory and practice and warns against excessive theorizing and the danger of psychoanalysis "to be over-flooded by a wave of theoretic speculation" (p. 58). This discussion, aimed at promoting the mutual benign enhancement of theory and practice, represents a step forward in sophistication of the psychoanalytic movement and by itself makes the monograph worthy of study.

Careful reading and rereading, however, leads to the increasing conviction that the authors were moving decisively toward a form of therapy which could no longer be characterized as Freud's psychoanalysis. The mixture or hodgepodge of treatment techniques that they predict will become increasingly prevalent in psychiatric practice bears little resemblance to the basic approach of Freud. In spite of their obvious understanding of the importance of countertransference, the authors do not seem to understand the effect of active techniques on the part of the therapist or of deliberate role playing, suggested at times to be necessary, on the formation of transference and its resolution.

There is a fascinating precursor of Kohut's notion of self-object transference involved in their concept that the patient seeks an "ideal parental imago . . . which we, however, cannot offer him permanently in the form in which he wishes it" (p. 21). But the authors do not recognize the intricacies involved in the management of this form of transference and the effect of the kind of activity they advocate on such a transference. Those psychiatrists who need background on the publication of this monograph or who wish some idea of the extremes to which it eventually led are advised to read the recent biography of Rank by Lieberman (1).

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Dream Interpretation: A New Approach. Classics in Psychoanalysis Monograph 5, *by Thomas M. French and Erika Fromm. Madison, Conn., International Universities Press, 1986, 224 pp., $25.00.*

The criteria by which different books are labeled classics in psychoanalysis are not made entirely clear in this series of reprinted monographs, edited by George H. Pollock. In this particular instance we are told by the editor that this book is not easily obtainable, although it came out originally in 1964 (1) and I have it in my library, as I would assume most older psychoanalytic psychotherapists do also. It presents what I consider an extremely controversial theory of dream interpretation that proposes in many ways to continue where Freud left off.

Although there are a few basic differences from Freud's approach to interpreting dreams, the main focus of this work by French and Fromm is on preconscious problem solving processes, which they visualize as taking place in what they call the "cambium layer" (defined on pages 187–188) of the mind—a metaphor borrowed without attribution from Freud (2, p. 444). In other words, the focus in this work is more on the ego processes involved in dream formation and less on the id processes or wishes that underlie the production of a dream, as Freud postulated and concentrated on. The authors attempt to focus on what they call the reactive motive in the wish and by so doing to understand better the kind of problem solving efforts that they postulate always goes on in the dreamer's thinking. This thinking, they claim, represents a struggle with concrete practical problems, not rational or verbal thinking but definitely intelligible and somewhat different from Freud's notion of primary process.

The authors maintain that every dream has many meanings, and they define the "cognitive structure" of a dream as the way these meanings fit together and "the way that they fit into the context of the dreamer's situation in real life" (p. 206). Thus, the cognitive structure of a dream is "a constellation of related problems" (p. 206), but each dream has a focal conflict, the one with the most cathected meaning, and a variety of subfocal conflicts. Furthermore, most of the

problems addressed are those of interpersonal adaptation. The patient's current problems in interpersonal adaptation "are sometimes identical with, and *always* derivatives of, problems in adaptation to the same or other groups in his past" (p. 60).

Thus, the purpose of dream interpretation is to get an increasingly comprehensive grasp of the cognitive structure of the dream. Defensive dream work, as the authors define it, makes this hard to do. For example, if the patient found the problem too disturbing, he or she may substitute an easier or analogous problem and work on that, or the patient may shift attention from one problem group to another or even attempt to wish away the whole matter and indulge in illusory wishful fulfillment.

An enormous number of epistemological assumptions are made throughout the book, ranging from a general theory of the development of thought processes to the authors' version of the validation of dream interpretation and empathic thinking. These are extremely controversial matters, as hotly debated today as ever, and the reader will have to decide whether he or she is convinced by the authors' argument. My own impression was that the argument requires further elaboration and that the concepts used are based on multiple theoretical assumptions, as the crucial diagram on page 168 and its accompanying discussion will readily demonstrate to the reader.

There is sure to be a chorus of objections from those who work in the fields of developmental epistemology, philosophy of science, and dream physiology to a number of the statements made by the authors. From my own clinical experience and teaching, an example of this is on page 125, where the authors describe their collaborative effort to validate their "interpretive reasoning." A patient's dream is presented, and "the group will begin piecing together suggestions offered, first by one and then by another, until finally, often rather suddenly, there emerges a solution that is satisfying to all" (p. 125). This kind of verification of dream interpretation, by the consensus of a group of psychiatrists so to speak, is a common practice among amateur "peer groups" and lies open to the powerful objection that it represents a form of "pop psychology" and the use of the dream as a Rorschach Test for the group participants. Whether the consensus about the interpretation is really relevant to the patient is not demonstrated by the fact that the group has reached a consensus.

It is interesting how close the approach of French and Fromm is to the current hermeneutic method and orientation toward the narrative of the psychoanalytic session, and of course the authors are to be praised for their serious effort to establish a methodology of verifying dream interpretations and their attempt to avoid what they call the "Procrustean bed" technique in which an interpretation is made on part of the evidence and all other material is forced to fit this interpretation. We must, say the authors, train ourselves "to be sensitive to gaps and discrepancies in our evidence" (p. 24).

The authors have also touched on some of the most important problems in the borderland between psychoanalysis and philosophy, borrowing, for example, Langer's distinction between the "discursive" use of language and the "creative speech" of a poet. Because his work was not widely known in the United States at the time the book was written, Heidegger is not mentioned, but his development of Langer's distinction as well as his claim that thinking begins with attempting to solve concrete practical problems in the everyday world are both assumed and used by French and Fromm. However, their Piaget-based view in chapters 12 and 13 on the development of thought processes, a fundamental assumption in their work, is far from generally accepted today.

This monograph is obviously mandatory reading for psychoanalysts and for psychiatrists who use dream interpretation as part of their psychotherapeutic work. I suggest reading the summary chapter 18 first in order to grasp most easily the many basic principles that are developed in the rest of the book. The unsophisticated reader should be warned that a number of statements regarding thinking, speech, and dreaming made by the authors are controversial. They have offered some sweeping generalizations about very complex thought processes alleged to go on ubiquitously in dreaming that will be extremely difficult to validate. It is best to test their approach in the crucible of one's own consulting room as one attempts to understand patients' dreams, and I think they would have heartily agreed with this conclusion.

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EPIDEMIOLOGY AND ECONOMICS

Mental Disorders in the Community: Findings From Psychiatric Epidemiology, *edited by James Barrett and Robert M. Rose. New York, Guilford Press, 1986, 377 pp., $39.95.*

This book presents lectures and discussion from the 75th annual meeting of the American Psychopathological Association, held in 1985. The proceedings of this conference have been published yearly since 1945, documenting the quality and endurance of the American Psychopathological Association. This particular volume targets psychiatric epidemiology for review and provides an international flavor to current research problems in the study of the distribution and determinants of mental illness in the population. Seventeen chapters are divided into five topic areas: The NIMH Epidemiologic Catchment Area Study, Lundby and Sterling County Studies, Epidemiology of Schizophrenia, Case Identification Methodology, and Implications for Policy and Program Planning.

The authors in this edited collection read like an international *Who's Who* of psychiatric epidemiology. The chapters generally reflect the excellent research background of the authors. Attention to detail and methodology are persistent themes. For example, in the Paul Hoch Award address, Erik Essen-Moller reflects on the beginnings of the Lundby Project, Sweden's major effort to evaluate the personality theories of Sjobring. Essen-Moller, along with three other psychiatrists, composed the interview team that personally interviewed 99% of a defined population of 2,550 persons during 2 months in the summer of 1947. The dedication of the investigators and the response rate they attained continue to serve as standards for researchers 40 years later.

The Presidential Address by Dr. James Barrett extends the focus on methodologic issues by examining the continuing problem of case identification among psychiatric disorders.

A lack of standardized diagnostic techniques with good measures of reliability and validity continues to be a major limiting factor of modern epidemiologic studies. Dr. Barrett emphasizes the need for longitudinal assessment measures, attention to characterological factors, and awareness that high kappa reliability consistency does not guarantee excellent validity.

Chapters in this book expand on the previously published journal literature. Each chapter is followed by questions and comments between participants and the lecturers. This style gives the reader a feel for the format of the American Psychopathological Association meetings—give-and-take sessions with opportunity for immediate feedback. When this format works, readers often wish they could jump in to ask another question or make additional comments. I often felt this way while reading this book. Individuals with an interest in psychiatric epidemiology will want to seriously consider this volume to add to published research articles in rounding out their reference libraries.

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Medical Care, Medical Costs: The Search for a Health Insurance Policy, *by Rashi Fein. Cambridge, Harvard University Press, 1986, 240 pp., $20.00.*

Professor Fein of Harvard University is the nation's outstanding advocate for equity in health care. In his writings he forcefully and articulately makes the case that the nature of our society and civilization is tested every time an individual is denied access to health care due to a financial barrier. More and more Americans lack private health insurance and do not have access to public insurance programs.

In *Medical Care, Medical Costs* Professor Fein traces the evolution of the victories and defeats of national health insurance in America. He describes the early rationale and struggles in the market for private voluntary insurance, the passage of Medicare and Medicaid, the different efforts at system reform, and the continuing structural problems of our health care system. The book is not only wonderfully technical but also contains a direct and compelling argument about the contending political philosophies: individual versus group, community versus exclusivity, and cooperation versus competition. These political forces and ideologies have faced each other over the past 75 years in American health care politics and continue today. The role of government in the delivery and financing of health care is also fully explored throughout the volume, but over and over again Professor Fein articulates the case for those who "have not" and the need for a national health policy as the twentieth century draws to a close.

Although the book never mentions insurance or coverage issues for mental illness, it is deeply relevant to Americans who have experienced mental illness or who have a family member in need of psychiatric care. Most health insurance plans cover mental illness but do so with added restrictions in benefits, "inside limits." These added visit and dollar burdens have created a crisis in access for Americans with severe mental illness. These individuals continue to burden our underfinanced public system for psychiatric care, which is in major need of overhaul and reform.

One cause of the crisis of mental illness insurance is the problem of "adverse selection." In discussing the problems of Blue Cross and Blue Shield in the competitive health insurance world, Professor Fein describes the dilemma of private third-party carriers and the provision of adequate psychiatric coverage:

> Competitive pressures were forcing Blue Cross to shift to experience-rated premiums that reflected the medical utilization of the particular enrolled group. The principle of community rating was giving way to the realities of the marketplace . . . . In a voluntary system with multiple sellers, people are free to chose with whom to pool risks and whether to subsidize their less fortunate fellows. An insurer who ignores this reality will lose more and more subscribers and will be left with the poorest health risks. (p. 53)

This problem led to the dramatic cutbacks in federal health benefits for mental illness in the early 1980s. The Blue Cross and Blue Shield high option program for federal employees was the only federal program in the 1980s that covered in a broad fashion both inpatient and outpatient psychiatric treatment costs. In 1975, the AETNA federal programs had cut back psychiatric benefits, and over a 5–6-year period high psychiatric treatment costs accumulated in the federal employees program of Blue Cross and Blue Shield. More and more people were leaving the high option Blue Cross program for lower-cost opportunities, which had extremely restrictive psychiatric benefits. It became uneconomical for Blue Cross and Blue Shield to continue its good psychiatric coverage in the high option program. The risks for catastrophic psychiatric illness were no longer spread to a large enough community. The principle of insurance was lost and the psychiatric patient suffered.

The new alternative delivery system approaches such as health maintenance organizations provide far less than adequate health insurance coverage for treatment of mental illness and the addictions, further segmenting the market and pushing the mentally ill toward the public hospital. States in turn respond by posing mandatory private insurance coverage. This accelerates the drive toward self-insurance, however, which does not have to abide by these limits. Psychiatric care, like most medical care, is costly, and unless the community pools its resources to pay for the unfortunate few in need of treatment, those few either will go without treatment (notice the mentally ill homeless on our streets) or will receive less care than is necessary and be reduced to a chronic burden on other parts of our social fabric, such as our jails or nursing homes.

This volume is a useful history and sets the stage once again for the articulation of a public policy that allows government to step in, redistribute resources, and make all of our lives more secure and fair.

The swing of the pendulum toward more market-based competitive approaches to health care with an emphasis on prospective payment has exacerbated the ongoing inequity as represented in uncompensated care and the phenomenon of increasingly medically indigent Americans. Professor Fein's book contributes to the current consideration of catastrophic health insurance, and it is up to providers as well as patients and families to assure that the mental health needs of Americans are reflected in the emerging national legislation in catastrophic care.

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LIAISON PSYCHIATRY

The Psychological Experience of Surgery, *edited by Richard S. Blacher. New York, John Wiley & Sons, 1987, 236 pp., $31.50.*

Let me tell you at the onset that this is a good book. Richard Blacher, the editor, who is also the author of three of its 13 chapters, is a highly regarded psychosomaticist and psychoanalyst. He is joined by a group of individuals who are experts in the areas covered by this volume.

There are some important omissions in the scope of the book, but it is clear that it is not the wish of the editor to deal with all pertinent areas. Being multiauthored, the style of the chapters vary. Bernard Meyer lets the reader know that his chapter, "On the Role of Denial in Cancer Surgery" is "lacking the systematic organization of usual scientific writing." His saving grace is his clinical experience and facile writing style, which is full of wit and literary reference. In contrast, Pietro Castelnuovo-Tedesco writes on "Bypass Surgery for Superobesity" with a model of scientific thoroughness in a 32-page chapter in which five and one-half pages are devoted to references. In further contrast, Judith Ellen Robinson writes "When Children Have Surgery" in only 17 pages with no reference beyond 1979.

However, as the editor states, the book does have unity in that it is written from the viewpoint of the patient. In doing this, all its authors use case material freely to illustrate the points they make and thereby add the dimensions of life and meaningfulness to this volume.

Dr. Blacher writes well in chapters on "General Surgery and Anesthesia," "Heart Surgery," and "Brief Psychotherapeutic Intervention for the Surgical Patient." To illustrate the usefulness of patient material, I will cite a case in his chapter on heart surgery. We are told of a 46-year-old chemist who is hospitalized for coronary bypass surgery. She has the persistent view that she will die during surgery despite reassurance from the medical staff that her prognosis is definitely excellent. Psychiatric interviews reveal that the patient's mother had died of heart disease and the patient, raised as a strict Catholic, believes that when her heart stops her soul will leave her body and go to heaven to join her dead mother. When the surgeon restarts the heart, she feels, she will then be in conflict between staying with her mother and returning to life. The revelation of this fantasy to the patient enabled her to consent to the operation and to undergo it uneventfully.

Peter Wilson and Mary Jane Schirger-Krebs write on "Psychological Factors in Lower Limb Amputations." Like the authors of other chapters, they have devoted years of clinical care and systematic research to the field they write about, and, like their fellow authors, their clinical experience is evident in the pertinence of the case material and in their meaningful discussion.

"Psychological Aspects of Breast Surgery" is well handled by Laurie Stevens. Malkah Notman's contribution, "Emotional Impact of Gynecological Surgery," deals with a subject that Dr. Notman knows well. In her characteristic style, she communicates clearly and succinctly, yet in depth. "The Psychological Adaptation to Renal Disease in Transplantation" is thoughtfully handled, but somewhat too briefly, by Samuel Basch, a pioneer in this area. Louis Linn addresses the almost neglected and fascinating subject of "Cosmetic Surgery With Particular Reference to Rhinoplasty."

This is a well-written, worthwhile book that should be part of every consultation-liaison psychiatrist's library and read by every psychiatrist, psychologist, and other behavioral professional interested in the psychological impact of surgery. It is a job well done by Dr. Blacher and his contributors.

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Liaison Psychiatry: Mental Health Problems in the General Hospital, *by Joan Gomez, M.B., F.R.C.Psych., D.P.M. New York, Free Press, 1987, 276 pp., $27.50.*

In this relatively brief volume the author presents a comprehensive review of the field of consultation-liaison psychiatry. The prose is succinct and the clinical material is described with clarity—in keeping with the best of British medical tradition.

The only concern that I have is with the organization of this book. There are 16 chapters arranged in a somewhat curious fashion. The beginning chapter is an overview and is followed by a chapter on assessment. Chapter three deals with psychological presentations in different disorders and chapter four with pain. Then follow chapters on the principles of liaison psychiatric practice in different disorders. For the most part these chapters are thorough and accurately presented. Separate chapters might have been given for cardiac and respiratory disorders, which are lumped as cardiorespiratory disorders in chapter six. The same might be said for dermatology and infections, which are joined in chapter 12. Chapter 14 deals with terminal illness and, with chapter 13, "Liaison in Oncology," represents an outstanding section of the book. Chapter 15 is a summary of pharmacology in liaison psychiatry. Chapter 16, "General Strategies for the Liaison Therapist," is helpful but does not describe principles of individual psychotherapy for these patients in adequate detail.

I would have found the book more useful had it been divided into three distinct sections. The first would include general clinical issues, theoretical concerns, and a framework for diagnosis and treatment of psychiatric disorders in medical patients. The second section would present specific disorders by organ system, which this book does to a substantial degree. The third section would attempt to synthesize the general with the specific, the theoretical with the clinical, and research with practice.

I was disappointed to see the brief space (one paragraph) allotted to psychiatric aspects of cardiac surgery. This section was the only one using dated references. In addition, the chapter on pharmacology might have been placed more strategically toward the beginning of the book following the section on psychological presentations of medical illness. Too few specific pharmacotherapeutic principles are given. A major concern of liaison psychiatrists is how to combine optimal pharmacotherapy and psychotherapy in dually diagnosed patients, and this book provides minimal help with that task.

The lack of research data on which to base the clinical recommendations is not a failing of the book so much as it is a critique of the field of consultation-liaison psychiatry. What little research has been done in this area might have been highlighted with suggestions for future studies to strengthen this clinical subspecialty.

One might argue that this book presents both the case for and the case against consultation-liaison psychiatry as a sub-

specialty field. There is definitely a body of knowledge in the field, but this knowledge is based perhaps too much on an unusual blend of theoretical constructs and common-sense practice, neither of which have had extensive or rigorous testing. Nonetheless, this book, in spite of its shortcomings, will be of use to residents rotating through consultation-liaison services, to medical students, and to candidates for Board examinations in the United States. It is also a fine clinical text for general internists and other physicians who wish to have some practical guide for managing psychiatric disorders in their patients. The book should be a stimulus to academic consultation-liaison psychiatrists and psychosomatic researchers to fill the wide gaps of knowledge suggested by this volume.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Carbamazepine-Induced Isolated Thrombocytopenia

SIR: Anemia and leukopenia are well-known side effects of carbamazepine. Isolated thrombocytopenia, a rare and yet potentially catastrophic complication, is less widely appreciated.

Mr. A, an 18-year-old student treated with phenytoin for generalized tonic-clonic seizures, contracted infectious mononucleosis, which was confirmed by a positive "monospot" and an elevated Epstein-Barr virus titer. Phenytoin was discontinued early in his illness because of concern that his symptoms were a drug reaction. A month later, treatment with carbamazepine was instituted, since Mr. A's blood and platelet counts had remained essentially normal during and after his illness.

Two days before starting carbamazepine, 200 mg b.i.d., Mr. A's baseline WBC count was 6,400/mm^3, his hemoglobin level was 14.7 g/100 ml, and his platelet count was 211,000/mm^3. On day 7 of treatment, the values were WBC count, 5,500/mm^3; hemoglobin level, 14.4 g/100 ml; and platelet count, 170,000/mm^3. The dose of carbamazepine was increased to 200 mg t.i.d., and on day 14 the WBC count was 5,600/mm^3, hemoglobin level was 14.2 g/100 ml, and platelet count was only 14,000/mm^3. The patient was asymptomatic, with no petechiae or bruises. Carbamazepine was immediately stopped. Platelet counts increased to 65,000 (day 16), 219,000 (day 19), and 378,000/mm^3 (day 26), with no change in WBC count or hemoglobin level.

We ascribe the thrombocytopenia to a depression of specific bone marrow elements by carbamazepine. Normal blood counts during and after the mononucleosis exclude that condition as the sole cause, although a synergistic effect of recent infection and drug exposure is possible.

We know of 10 other cases of isolated thrombocytopenia occurring with carbamazepine treatment (1–3). In seven of eight cases in which the time course is known, thrombocytopenia occurred during the first month of therapy (personal communication, Dr. P. Gibney, CIBA-Geigy Corp.). Although the manufacturers advise frequent laboratory testing of patients taking this drug, many physicians apparently do not follow these recommendations. Some authors (4) feel that such tests are excessive in number, frequency, and cost. Platelet counts have been omitted from laboratory monitoring of carbamazepine therapy in reported cases (5).

Carbamazepine-induced bone marrow suppression is rare, but with the increasing use of this drug in psychiatric as well as neurologic practice, a larger number of potentially fatal reactions can be expected. The risk of bone marrow suppression appears to be greatest in the first few weeks of therapy. Our report underscores the importance of frequent monitoring of platelets as well as blood counts during this period. This case also suggests the possibility that certain infections may potentiate the hematologic toxicity of carbamazepine.

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Combined Drug Therapy for an Elderly Depressed Patient

SIR: We wish to report the case of an elderly woman with a refractory depression who finally responded to a combination of doxepin, phenelzine, and lithium without untoward effects.

Ms. A, a 71-year-old widow, presented with a 1½-year history of increasing depression following the death of her husband. During this time she had received two separate courses of ECT, with some response, but her condition would deteriorate almost immediately after the course ended. She manifested vegetative symptoms and mood-incongruent delusions of persecution. Her past psychiatric history revealed recurrent episodes of depression for 30 years, with eight hospitalizations in the past 10 years. Previous treatments with nortriptyline, doxepin, imipramine, thioridazine, perphenazine, and lithium had been unsuccessful. All previous episodes had been terminated by ECT, but even maintenance ECT for 6 months had failed to prevent relapse.

It was decided to aggressively pursue pharmacotherapy, since ECT had not provided sustained remission of symptoms. Initial treatment with phenelzine, 30 mg b.i.d., and haloperidol, 2 mg b.i.d., produced some evidence of improvement, but the dose of phenelzine had to be reduced to 15 mg b.i.d. because of severe orthostatic hypotension that could not be controlled by fludrocortisone. Six weeks of this regimen, followed by the addition of lithium carbonate, 450 mg/day, for 4 weeks, produced no symptom relief. A subsequent trial of 5 mg b.i.d. of methylphenidate alone only exacerbated Ms. A's agitation.

Because of her initial improvement when she had taken the higher dose of phenelzine, a trial of combined monoamine oxidase inhibitor (MAOI) and tricyclic was considered. Doxepin was started and then increased to 50 mg h.s. Four days later, phenelzine, 15 mg every morning, was introduced. Because of continuing persecutory ideation,

haloperidol, 3 mg/day, was added. The doxepin was then increased to 75 mg h.s. Ms. A's sleep and appetite improved, but she continued to feel lethargic and depressed. Her orthostatic hypotension limited further increases of these medications, so lithium carbonate, 300 mg h.s., was added. After 3 weeks of taking this combination, with 12-hour lithium levels of 0.32 meq/liter, her condition was unchanged, so the dose of lithium was increased to 450 mg h.s., which resulted in a lithium level of 0.86 meq/liter.

Within 1 week, Ms. A improved rapidly, becoming more animated, energized, and euthymic. She was no longer psychotic, so the haloperidol was discontinued. At the time of this writing, she was living independently and had had complete symptom remission for 9 months without adverse sequelae.

Ms. A failed to respond to any combination of lithium and an antidepressant (tricyclic or MAOI) and to a tricyclic and an MAOI in combination. The role of lithium augmentation of tricyclic antidepressants is becoming increasingly substantiated (1, 2). Preliminary results from studies exploring its efficacy with MAOIs also appear favorable (3, 4). MAOIs and tricyclics in combination have been demonstrated to be safe and effective (5). When all of these treatments fail in refractory depression, we feel that it is worth considering all three in combination. Even in an elderly patient, they were well tolerated and provided complete symptom resolution. Concerns over polypharmacy in geriatric patients have to be balanced against the potential benefits of multiple-drug regimens in the treatment of refractory depression.

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Tolerance of a High Dose of Haloperidol by an Elderly Patient

SIR: Elderly psychiatric patients usually require smaller doses of psychoactive medication than younger patients. The following case illustrates a remarkable exception to this rule.

At age 73 Mr. A had suffered from paranoid schizophrenia for 43 years. He had never married, had no family, and lived in boarding homes. Serious suicide attempts had resulted in several previous hospitalizations. During his last admission, 4 years previously, his chronic psychotic symptoms had failed to respond to 10 ECTs or to a 6-week course of trifluoperazine, 40 mg/day, which had induced little other than marked sedation. At discharge it was felt that, because of his age, he would not tolerate higher doses of a neuroleptic and he would remain chronically psychotic.

Mr. A's condition slowly deteriorated to the point where he was living in squalor. On readmission to the hospital, he was anxious, angry, and guarded but compliant. There was choreoathetotic movement isolated in his right hand, which was suspected to represent tardive dyskinesia. He complained that "forces" were pushing thoughts into his brain and that "gangster voices" were laughing and talking about him; he feared they might tell him to kill himself. He sat in his room in the dark. When he was given haloperidol, 30 mg/day p.o., the only clinical change was full suppression of the dyskinetic hand movements. He suffered a mild anteroseptal myocardial infarction 2 months after admission but recovered fully.

Over a 6-month period, Mr. A's dose of haloperidol was slowly increased to 100 mg/day, and procyclidine, up to 22.5 mg/day, was added for akathisia. The patient's fear slowly decreased, and he reported feeling more comfortable, with prolonged hallucination-free periods. He started leaving his room, took care of his personal appearance and hygiene, and smiled and interacted appropriately with others. His only complaints were dry mouth and laxative-responsive constipation. There were no other autonomic or neurological symptoms. His cardiac status remained stable. His serum prolactin level was 58 ng/ml (twice the upper limit of normal) and there were no breast changes. The results of all other blood tests remained within normal limits. Without Mr. A's knowledge, two subsequent attempts were made to reduce his dose of haloperidol to 90 mg/day. Each time he eventually reported increased anxiety. He had been taking haloperidol, 100 mg/day, for 6 months. The procyclidine was gradually discontinued. The possible risks of prolonged use of very high doses of haloperidol were explained to Mr. A, but he insisted on continued treatment.

Despite the great range of effective therapeutic doses of neuroleptics for paranoid schizophrenia, Mr. A required and tolerated an exceptionally high dose, especially for a geriatric patient. While there remained concern about neuroleptic malignant syndrome (1), dystonia, tardive dyskinesia, delirium, and hypotension (with risk for stroke or repeat myocardial infarction), his mental, physical, and social status were at the best they had been in years. Although this case in no way represents an endorsement of routine high-dose neuroleptic treatment in chronically psychotic geriatric patients, one should not give up until treatment has been pushed to tolerance or effectiveness.

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A Case of Lithium Carbonate Abuse

SIR: While reports of lithium intoxication and overdose are common (1), to our knowledge, save for a general warning about lithium abuse among polydrug abusers (2), a case of lithium carbonate abuse has not been reported. We would like to relate one such case.

Mr. A, a 54-year-old white man with a long history of bipolar disorder and chronic alcohol abuse, had been followed at our community mental health center and maintained on a regimen of lithium carbonate, 600 mg. t.i.d., as well as thioridazine, 100 mg t.i.d.; his lithium level was generally 0.8–0.9 meq/liter. He reported drinking wine, usually one bottle, on days when he could afford to buy it. Approximately 2 weeks before admission to the hospital, Mr. A reported that family members had refused to give him money for wine, and he had tried to get high by other means. He started taking, at times, approximately 2400 mg/day of lithium (instead of the prescribed 1800 mg/day) "for a buzz." He later discovered that taking the lithium with about three cups of coffee in the evening relaxed him and led to feelings of light-headedness and giddiness.

After taking this combination a number of times, Mr. A felt ill. He went to an emergency room, where his lithium level was noted to be 3.0 meq/liter. Shortly thereafter he was admitted to our inpatient service, ataxic and somnolent. His lithium level shortly after admission (more than 36 hours after his last ingestion of lithium) was 1.9 meq/liter. A urine drug screen produced negative results, as did a test of his serum alcohol level. He underwent an uneventful lithium detoxification. He was then restarted on lithium and discharged on a regimen of lithium, 600 mg t.i.d., and chlorpromazine, 100 mg at bedtime. His lithium level at discharge was 1.0 meq/liter. When he was seen later, he reported no desire to overmedicate with lithium.

Self-intoxication with lithium by an alcohol abuser is interesting because lithium has been suggested as a treatment for alcoholism (3). Our patient's concurrent use of coffee probably reflected a simple combination of the stimulant effects of caffeine with lithium intoxication, since caffeine would be expected to lower lithium levels by virtue of its diuretic effect. It would be interesting to determine whether this is simply an isolated incident or reflects a more general pattern of lithium abuse.

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Intractable Hiccups Treated With Amitriptyline

SIR: Hiccups are intermittent spasmodic contractions of the diaphragm. Persistent hiccups (singultus) can not only be embarrassing and physically exhausting but can lead to serious medical problems. We present the cases of two patients treated successfully with amitriptyline. We have not treated any other patients for intractable hiccups.

Mr. A, a 37-year-old man with a 4-year history of chronic hiccups, had been treated with chlorpromazine, metoclopramide, ranitidine, diazepam, and an antacid without success. He had about seven episodes of hiccups per day and would occasionally be awakened by them at night. He frequently had difficulty eating and had lost 30 lb over the past year. His history revealed alcohol abuse and recurrent pancreatitis. An extensive inpatient workup included an examination of the upper gastrointestinal tract, upper endoscopy, abdominal ultrasound, and an abdominal computerized tomography (CT) scan. The results of these procedures were essentially normal except for a small hiatal hernia and esophagitis. Mr. A was discharged on a regimen of ranitidine, 150 mg h.s., and was referred to the psychiatry service for an evaluation of a possible psychophysiologic reaction. After extensive diagnostic interviews by two psychiatrists, it was felt that no current psychiatric diagnosis could be made. No psychological testing was done.

Mr. A was then started on amitriptyline, 10 mg t.i.d. and 25 mg h.s. Within a week he noted a marked decrease in his hiccups. He was having only two to three mild episodes a day and none at night. He was unable to tolerate higher doses of the medication because of side effects. He continued to do well for 3 months, after which time he failed to keep follow-up appointments.

Mr. B, a 64-year-old man with a 25-year history of persistent hiccups, had been treated with chlorpromazine and carbamazepine without gaining relief. For the past 2 years his hiccups had been almost constant during the day, and he had a great deal of difficulty talking on the telephone. He had a history of hypertension, hypercholesterolemia, coronary artery bypass surgery, and alcohol abuse. His medications included aspirin, 325 mg/day; propranolol, 20 mg q.i.d.; and furosemide, 20 mg/day. An extensive workup included an examination of the upper gastrointestinal tract, esophageal manometry, and an upper endoscopy. The findings on these tests were essentially normal except for a small hiatal hernia. A CT scan of the head revealed a small right parietal infarct.

Mr. B was referred to the psychiatry service because of "psychogenic hiccups." Extensive interviews were conducted in the same manner as in the case of Mr. A, and again no current psychiatric diagnosis could be made. The patient was started on amitriptyline, 10 mg t.i.d., with a gradual increase to 50 mg b.i.d. over 2 months. He reported an 80% reduction in the intensity and frequency of his hiccups. A brief increase in the dose of amitriptyline to 150 mg t.i.d. resulted in a worsening of his hiccups, so it was reduced to 50 mg b.i.d. Mr. B continued to do well 5 months after the initiation of treatment and had only mild hiccups, which occurred primarily in the evening.

Intractable hiccups may be a symptom of a metabolic, abdominal, thoracic, or CNS disease (1). Some of the common disorders that are thought to cause hiccups include hiatal hernia, esophagitis, pancreatitis, and alcoholism. Both of our patients had a history of alcohol abuse and hiatal hernia. The first patient had all of the problems we have just mentioned. Multiple pharmacologic treatments for hiccups

have been suggested, including chlorpromazine, haloperidol, metoclopramide, benzodiazepines, carbamazepine, and phenytoin. A few reports have indicated that low doses of amitriptyline are successful. One early report of eight patients (2) noted that 25 mg/day of amitriptyline produced total relief in four patients and partial relief in three. These patients had various etiologies for their intractable hiccups. Only three of the case reports provided data on the duration of the hiccups. In two patients the duration was less than 3 months, and both patients appeared to gain complete relief with amitriptyline, although one was lost to follow-up. In the third case the duration was 3 years, and the patient's relief was only partial. A more recent report (3) indicated total relief with 30 mg/day of amitriptyline in a patient whose hiccups had persisted for a year.

Both of our cases were of relatively long duration (4 and 25 years), which may have made the treatment more difficult. Amitriptyline is rarely mentioned as a treatment for persistent hiccups, but it should be considered. Doses as low as 25 mg/day can be effective; however, higher doses may be needed.

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Female Hypersexuality Treated With Cyproterone Acetate

SIR: The use of cyproterone acetate to treat male hypersexuality is well documented (1). We describe the successful treatment of a hypersexual woman with this drug after other treatments had failed.

Ms. A, a 40-year-old single woman, started having sexual intercourse at 12 years of age. Experiencing orgasm from the first, she soon developed a preference for multiple orgasms, with successive sexual partners, but usually supplemented their efforts by masturbating. This behavior continued throughout her adolescence. At age 20 she sought psychiatric help, because her sexual behavior conflicted with her religious beliefs and her relationships with men seemed meaningless. During the next 10 years she had individual psychotherapy, behavior therapy, and courses of antidepressants, neuroleptics, and benzodiazepines with little effect. At age 31 she sexually assaulted a man. Frightened by this, she gave up psychiatric treatment and sexual relations. She masturbated six to eight times daily and avoided male company, but violent erotic dreams disturbed her sleep. Little changed during the next 9 years; she lived alone, had the same job, and had a few female friends from her church.

Ms. A then sought help again, because changes at work had involved contact with young boys and she feared that she might sexually assault them. Her previous medical, psychiatric, and family histories were unremarkable, and the results of a physical examination, including a gynecological examination, were normal. Extensive investigations of the CNS and endocrine system also resulted in normal findings, particularly her serial testosterone and free testosterone levels.

The patient's need for reduction in libido and her hypersexuality without evident cause led to a trial of the antiandrogen agent cyproterone acetate. Ms. A was given 50 mg/day of this drug on days 5–15 of the menstrual cycle and ethinyl estradiol, 50 μg/day, on days 5–25. Within a few days she stopped masturbating, the erotic dreams ceased, and males did not evoke sexually aggressive feelings. Six months later she developed hypoglycemia and these medications were stopped. Within 4 weeks her hypersexual behavior returned, and it remained unchanged for 3 months. Then, following the diagnosis and treatment of lactose intolerance, cyproterone acetate and ethinyl estradiol were restarted, with equal effect. The dose of cyproterone acetate was then reduced to 25 mg/day; the dose of ethinyl estradiol was unchanged. Ms. A has remained symptom free for the past 6 months, and her endocrine function is unchanged.

In a review of female hypersexuality, Levine (2) noted that the condition is uncommon and, while speculation is rife, little is known about its cause. We cannot find any other accounts of the use of cyproterone acetate to treat this condition. However, reduced libido is a recognized complication of its use in treatment of female hirsutism (3). Cyproterone acetate is a 17-hydroxyprogesterone derivative that weakly inhibits androgen production, but its main mode of action is the blockade of androgen receptors. The dramatic effect of this drug, confirmed by stopping and restarting it, in a woman with normal androgen levels leads to our postulating that the cause of her hypersexuality was a proliferation, or hypersensitivity, of androgen receptors. Indirect support for this hypothesis comes from an observation that hypersexuality in delinquent girls is associated with exposure to exogenous androgens early in life (4).

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Hemifacial Flushing During Unilateral ECT

SIR: We should like to present the following case report.

Ms. A, a 16-year-old right-handed female, was hospitalized with symptoms of catatonia of 9 months' duration.

We began to treat her with right unilateral ECT after she failed to respond to sequential treatment with neuroleptics, imipramine, and phenelzine.

Electrical stimulation of the brain was done with a Medcraft ECT machine and resulted in visible seizure activity in the patient's left upper arm, to which a tourniquet had been applied. During the second right unilateral ECT session, we happened to observe that the patient's face and neck were flushed *only* on the right half (ipsilateral to the treatment side), with a clear midline demarcation of the flushing and elevated skin temperature, and only her right eye was congested and lacrimating. We continued to notice the same phenomenon during the next four right unilateral ECT sessions. After deliberations with colleagues, we gave Ms. A one left unilateral ECT, using the same machine, voltage, and electrode placement. We then noted that the patient's face and neck were flushed only on the left side and that only her left eye was erythematous and lacrimating.

Magnetic resonance imaging of Ms. A's brain did not reveal any structural abnormality. We then began to treat her with bilateral ECT because of the lack of improvement of her symptoms. During the five bilateral treatments, we observed that her entire face was flushed and she exhibited the eye signs on both sides. The patient's catatonic symptoms improved slightly after the bilateral treatments, and she was discharged from the hospital a few weeks later.

Flushing of the face and eye signs seen during ECT are a result of increased parasympathetic activity following electrical stimulation of the brain. The literature on ECT indicates that this is a central autonomic response (1). In our collective experience of administering well over 500 unilateral treatments, we have always observed this response on both sides of the body in a symmetrical manner, even after administration of unilateral ECT. The repeated lack of such an expected response in our patient can be explained by the following concept. We hypothesize that the increased parasympathetic activity that follows electrical stimulation of the brain is not a central effect alone but a result as well of stimulation of the vagus nerve (which supplies cholinergic fibers to facial blood vessels), its ganglia, and intercommunicating ramus (2) with the facial nerve (which supplies the lacrimal gland) and/or the carotid sinus, as a local or peripheral effect of passage of electrical current through these structures. For unknown reasons, our patient did not have the centrally mediated parasympathetic response but had an intact local or peripheral response on both sides. We believe that unilateral electrode placement evoked this response on each side, producing the ipsilateral facial and eye signs. When we gave the patient bilateral ECT, the same peripheral response was evoked, albeit on both sides.

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Long-Term Claustrophobia Following Magnetic Resonance Imaging

SIR: Recently, the advantages of magnetic resonance imaging (MRI) have made this procedure popular. Unfortunately, the physics of the apparatus require the patient to lie totally enclosed in a long dark tube, separated from the curved ceiling by only centimeters and unable to see outside (1). This often elicits the sensation of being confined in a tomb. It is therefore claimed (1) that 1%–5% of all patients receiving MRI experience transient claustrophobia. The patients we shall describe had no history of claustrophobia and were able to tolerate MRI, but after the procedure they noted a persistent inability to tolerate enclosed spaces such as elevators, i.e., claustrophobia. To our knowledge, this is the first report of persistent claustrophobia in previously nonclaustrophobic persons following MRI. The phobias were discovered through routine psychiatric examinations approximately 3 months after MRI, on admission of the patients to the University of Miami Comprehensive Pain and Rehabilitation Center.

Mr. A was a 24-year-old single white man with a chronic pain problem of 6 months' duration who had no previous psychiatric history. However, his mother suffered from claustrophobia. Mr. A claimed that he had been in the scanner for 3 hours, and because his head couldn't move he became progressively more anxious. After the procedure he could not tolerate any enclosed space, most specifically elevators, and had to use stairs no matter how high he had to climb. The results of a psychiatric examination were within normal limits except for anxiety associated with the chronic pain and the isolated phobia. There was no history of panic attacks or agoraphobia.

Ms. B was a 39-year-old married woman with a chronic pain problem of 5 years' duration. At age 29 she had a depressive episode that required treatment with medication. On index evaluation she was depressed and anxious and complained of marital difficulties. She had no previous history of panic attacks or agoraphobia. Her claustrophobia was not associated with the depression but began immediately upon her entrance into the scanner and continued to intensify during the procedure, which she finished only through sheer willpower. After the MRI she was unable to enter elevators and was fearful of any enclosed space—including automobiles, which she was able to tolerate only because the windows could serve as exits.

While they were being treated for chronic pain, both of these patients were also treated for claustrophobia by means of systematic desensitization, first in vitro and then in vivo. For both patients, the claustrophobia resolved, and the resolution was maintained at 6-month follow-up.

The sequence of events outlined by the two patients appears to implicate MRI as the possible cause of the claustrophobia. Some authors believe that this type of conditioning experience triggers a phobia, while others believe that verbal or vicarious experiences (2) are the triggers. Genetic factors may also play a role in the strength and content of phobic fears (3). Our two patients did not fit into the typical age groups for the development of phobic fears. The peak incidence of enclosure fears (claustrophobia) occurs in persons under 15 years of age (4); the median age at onset of simple phobia is 12 years, and the mean age is 16 years (5). We believe that this report should serve as a stimulus for a more

systematic investigation of the possible incidence of persistent claustrophobia following MRI.

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New Information on Polydipsia and Hyponatremia in Psychiatric Patients

SIR: We wish to add information to our recently published article "Polydipsia and Hyponatremia in Psychiatric Patients" (1) that was not available at the time the article went to press. In discussing the factors that might lead to the development of hyponatremia in polydipsic patients, we included the syndrome of inappropriate secretion of ADH, neuroleptic and other medications, a "reset osmostat," and local renal factors. We mentioned that chronic fluid loading might in some way cause a renal supersensitivity to normal or low levels of ADH. At the time we wrote our article, there was no direct evidence of such supersensitivity; several authors had instead documented elevated, rather than low, levels of ADH in these patients.

A recent article in the *New England Journal of Medicine* (2), however, shows that renal supersensitivity may indeed be present. Goldman et al. carefully compared psychiatric patients with and without polydipsia and hyponatremia. Their study shows impairment of urinary dilution in the presence of adequate suppression of ADH. Thus, it appears that renal supersensitivity to ADH may indeed contribute to the development of hyponatremia in polydipsic psychiatric patients.

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Laws on Mandatory Reporting of Suspected Child Sexual Abuse

SIR: An initiative is under way in some states to enact legislation mandating that psychiatrists report patients who acknowledge sexual involvements with children. Although this may seem a good idea, more careful reflection brings concern.

Physicians are expected to apprise patients through "informed consent" of the potential risks involved in seeking and receiving care. With mandatory reporting, physicians may have a responsibility to inform patients that information they reveal can be used against them (i.e., a Miranda warning), that sexual offenses are potentially punishable by incarceration, and that information they provide may become part of the public record. Few attorneys consulted by patients would recommend self-incrimination.

Statutes that mandate reporting by physicians who examine youngsters do not involve a conflict of interest with the child patient. However, reporting statutes that deter pedophiles from coming forward and deter candor in therapy may deprive children of their right to be at less risk. At The Johns Hopkins Hospital, a number of persons have come forward annually to seek help only after being reassured that reporting was not required. Many in treatment have self-reported relatively minor problems, allowing intervention before the problems have become more serious. By receiving information, clinicians are often able to intercede and protect children, even when they are unable to aid the children directly. When patients are deterred from providing such information, this is not possible, and the risk to children may be increased.

Reporting laws compel psychiatrists to act as state agents, probably in violation of the Hippocratic oath. When such laws compromise patients' candor, physicians may lose their capacity to treat effectively and to ascertain treatment efficacy. It is physicians and health workers who are singled out, since most reporting statutes exclude attorneys, paralegals, and clergy. If some physicians wish to ask patients to waive confidentiality voluntarily, this is acceptable, but reporting statutes compel all physicians to act as state agents without discretion.

Reporting laws compel some individuals to self-incriminate in order to receive needed care. Persons deterred from seeking care may be at increased risk of violating the law by not getting that care and are placed in a double bind. Frequently, reporting statutes have been implemented without first trying less intrusive measures such as limited immunity. Often, when patients have been reported, informed consent was not given.

The states have not proven that reporting laws increase the numbers of youngsters helped, yet patients are required to give up their right to privacy, to not incriminate themselves, and to freedom of speech without fear within the patient-physician relationship. In Maryland, proposed legislation speaks of pedophilia and may discriminate against a specific category of patients. Recently, the American Civil Liberties Union has expressed concern.

In considering the protection of youngsters, it is important to contemplate what legacy will be inherited by the next generation. A society in which patients are afraid to seek treatment and speak openly in it, a society in which physicians are mandated to act as state agents and gather information that may be used to incarcerate, a society in which children may be at increased risk because others fear coming forward may not constitute a legacy to be viewed with pride.

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Zar: A Traditional Method of Healing in Africa and the Middle East

SIR: *Zar* is one of the successful primitive techniques of mental healing. It was first introduced to the Middle East from Ethiopia, where it originated among the Cushite tribes, although Modarressi (1) attributed its origin to Iran. In Ethiopia the word *zar* means possessing spirit; in Arabic it means visited, implying the visit of a wicked spirit, devil, Satan, or *djenne*; in the Farsi language it means crying attributed to a severe depressive state.

Africans believe that beauty renders certain women vulnerable to possession by the *zar* spirit. During such a state the spirit, or *djenne*, has sexual intercourse with his human victim, following which the patient withdraws from society, becomes lonely, shows a mixture of apathy and depression, and may become dissociated—pacing, screaming, and running about wildly. The *zar* spirit may start talking through the mouth of the possessed, and the victim will be in a state of hysterical trance, which is followed by temporary amnesia. Sometimes several spirits or *zars* may possess one patient, who will be seen talking to each one with different tones of voice.

The *zar* ceremony is performed by a healer who has different names. In Ethiopia he is a Coptic priest, in Iran he is a *baba*, in Africa he is a witch doctor, and in Arabic countries he is a *kaudia*. The initial ceremony lasts for about 4–8 hours but may last up to 2 days. The patient dresses as a bride and fasts until the ceremony ends. One of the women adopts the role of leader; she wears rich and colorful clothes and carries a sword. The healer gives the order for the rhythmic beating of the drums to start, and the leader leads the group in a dance with the patient in the center. They continue dancing nonstop until they all reach a trancelike state and their dancing reaches a peak of emotional excitement, at which point the patient falls to the ground in a frenzy, followed by collapse. Once awakened, the patient experiences a loss of memory of her abnormal patterns and a return to her healthier self. The sudden and dramatic collapse is referred to as "little death," referring to the symbolic death of the old personality and sudden departure of the possessing spirit. To celebrate the cure, the healer orders the sacrifice of a chosen bird, and the patient is given its blood to drink.

The spirit is never exorcised but is likely to manifest itself in future *zar* rituals or in the form of further sickness (2). The immediate relief is dramatic, and nearly all patients who attend the *zar* rituals on a continuous basis stay free of symptoms. Okasha (3), in a survey of 100 Egyptian women, found that all who attended *zar* rituals were between 10 and 59 years of age; most were in the 30–50 age group, were married, and were unhappy, with marital disharmony and sexual dissatisfaction. Over half of this group were hysterics; three-quarters were housebound, had a positive family history of similar complaints of insomnia, depression, and hypochondriasis, and showed above-average response to *zar* treatment. El-Islam (4) studied the phenomenon in 60 women in Persia who were living under harsh social conditions and lacked a nuclear family because they were divorced or widowed and had no children.

In conclusion, the *zar* ritual, which induces a state of intense excitement that rises to a peak to the sounds of rhythmic drumming and is followed by collapse, is described as similar to the effects of unmodified ECTs (5).

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Psychiatric Disorder and Endometriosis

SIR: In their recent paper on the relationship between bipolar mood disorder and endometriosis (1), Dorothy Otnow Lewis, M.D., and associates reported finding definite affective disorder in 12 of 16 consecutive patients treated for endometriosis at a university hospital women's clinic. They suggested a possible hormonal link between the two disorders. They did not consider an equally important linkage, the influence of psychiatric illness on the reporting of symptoms. Bipolar illness may be frequently present among endometriosis patients not because they have a higher prevalence of anatomic lesions but because they perceive and report more symptoms. The authors assumed that receiving treatment for endometriosis depends only on the presence or absence of pelvic pathology. They ignored the intervening influences of individual variation in symptom perception and help seeking.

Various sources support the view that psychiatric disorders are linked with increased reporting of physical symptoms and greater use of medical care. Data from the Epidemiologic Catchment Area study (2) showed that subjects with *DSM-III* diagnoses used medical care more frequently than those without. Patients with anxiety and affective disorders demonstrate decreased pain tolerance, increased sensitivity to bodily sensations, and increased utilization of medical care (3). A paper in this journal (4) specifically addressed the influence of psychiatric disorder and emotional distress on seeking treatment for pelvic pain. That study found that patients presenting for evaluation of pelvic pain had a severity of pelvic pathology (endometriosis and/or adhesions) indistinguishable from that of asymptomatic patients. Patients who sought treatment for pelvic pain, though, were distinguished from asymptomatic control subjects by higher frequencies of depressive disorder, substance abuse, sexual dysfunction, and childhood sexual abuse. The authors concluded that "for most women with pelvic pain the pathological findings have little or no relevance to the chronic pelvic pain, which is due primarily to the past and present psychological problems of the patient." Had this study not been controlled by laparoscopy of the asymptomatic women, one might conclude that depression, substance abuse, and sexual abuse are etiologically related to endometriosis. The controlled design revealed instead that psychiatric diagnosis and emotional trauma are related to reporting symptoms and seeking care.

The study reported by Dr. Lewis and colleagues would benefit from similar control data. Laparoscopy of asympto-

matic women would demonstrate whether or not they had a severity of anatomic pathology similar to that of the patients. These data would allow conclusions about whether affective illness is hormonally related to endometriosis or instead related to reporting symptoms of pelvic pain and receiving treatment for endometriosis.

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The Spectrum Concept and Prevalence of Neuroleptic Malignant Syndrome

SIR: The rigorously designed prospective study by Paul E. Keck, Jr., M.D., and colleagues (1) provided interesting information on the prevalence of neuroleptic malignant syndrome in view of the recent controversy (2–4). The results confirmed the apprehensions that the syndrome has been overdiagnosed in some of the retrospective studies (3, 5). A prevalence of 0.9%, as suggested by Dr. Keck and coworkers, is much closer to the often cited estimate of 0.5%–1.0% (6). Both of these are in sharp contrast to the prevalence rate of 12.2% estimated by Addonizio et al. (2). I agree with Dr. Keck and his associates in believing that one reason for bias in retrospective studies is the likelihood of misinterpreting severe extrapyramidal symptoms as neuroleptic malignant syndrome. It is interesting to note that the prevalence did not increase despite earlier recognition of milder cases as a result of heightened awareness of the condition (1). Even when evaluated under such rigorous conditions, the prevalence is in the area of 1% rather than 12%, as suggested earlier (2, 4).

Besides an overinclusive definition of the syndrome, undue reliance on elevated creatine phosphokinase values alone may also have been responsible for the high prevalence estimates in retrospective studies. The diagnostic value of an elevated creatine phosphokinase level, which has been given the sacred status of a major or essential criterion, needs to be viewed in light of its lack of specificity. Absence of a thorough medical workup of febrile illness may also give such inflated figures, especially in retrospective studies.

However, I do not agree with Dr. Keck and colleagues in concluding that their results corroborate the spectrum concept of neuroleptic malignant syndrome (2, 4). The essence of the spectrum concept is visualization of the syndrome as an extension of extrapyramidal symptoms. This approach suggests that the symptoms of neuroleptic malignant syndrome, often without marked elevation of temperature, can stop without cessation of neuroleptic treatment (2). Such an approach may inadvertently cause the clinician to adopt a careless attitude toward management of the syndrome (5). Indeed, the spectrum concept is an artifact of an arbitrary definition and sidetracks certain important clinical issues (5). In my view, the findings of Dr. Keck and associates have produced an indirect challenge to the validity of the spectrum concept, rather than corroboration of it.

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Hoigne's Syndrome and Doom Anxiety

SIR: Stephen M. Saravay, M.D., and associates (1) recently observed that fears of impending doom or the belief that death has occurred are specific manifestations of lidocaine toxicity. Silber and D'Angelo (2) noted the similarity between these manifestations and Hoigne's syndrome. I had originally suggested the possible relevance of anomalous dominance, prostaglandins, and thromboxane to the etiology of Hoigne's syndrome (3).

My colleagues and I are presently investigating whether anomalous dominance is related to acetylator status in normal control subjects. Recently, we had the case of an 18-year-old male soldier who developed psychosis and seizures following the injection of penicillin G procaine and who had a high score on the Healey questionnaire measuring anomalous dominance.

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The Phase-Shift Hypothesis of Seasonal Affective Disorder

SIR: We do not agree with Frederick M. Jacobsen, M.D., and colleagues that the data in their article "Morning Versus Midday Phototherapy of Seasonal Affective Disorder" (1)

refute our phase-shift hypothesis, which states that one of bright light's effects in the treatment of patients with winter depression is related to its causing a phase advance in circadian rhythms relative to sleep and which attributes the superior antidepressant response of morning light in these patients to a corrective phase advance. Because phase-response curves with dead zones during the day have not been demonstrated in humans and, more importantly, because the phase-response curves of patients who are depressed in the winter may be phase delayed (a point noted in the Jacobsen et al. article), the noon light exposure that Dr. Jacobsen and co-workers used could be capable of causing a phase advance. We have shown that morning light (which causes a corrective phase advance) is significantly more antidepressant than evening light (which causes a phase delay) (2). It is curious that, despite their extensive experimentation, Dr. Jacobsen and associates have never made this comparison. (We have reviewed the literature on light therapy elsewhere [3].)

Given the fact that posttreatment Hamilton Rating Scale for Depression scores in the study by Dr. Jacobsen and colleagues were still within the symptomatic range and given the absence of a placebo control group (since neither the patients nor probably the raters were blind to which were the baseline weeks), the study is a textbook example of a setup for a type II error. The question still remains: Why was morning light in the Jacobsen et al. study not as effective an antidepressant as it was in our study? In our study the patients had morning light therapy immediately upon awakening. This was apparently not the case for many of the patients in the study done by Dr. Jacobsen and associates. Thus, their study could have been comparing two "midday" light conditions.

The lack of a difference between the effects of the treatments might also have resulted from the fact that some patients apparently received exposure to sunlight en route to work. Although the authors mentioned that their patients kept light exposure logs, they did not present the data. The authors also did not report Hamilton depression scale data from the final withdrawal week, which would have been helpful in evaluating the possibility of an order effect to determine whether patients were gradually improving over the course of the study. The difference between treatments might also have been obscured by a large placebo component. Although the authors argued that the poor correlation between patients' predictions and which treatment was more effective is evidence against a placebo effect, this is not a meaningful analysis, since one treatment was *not* more effective than the other. Ironically, by the authors' own criteria, a substantial placebo response appears to have been present in their study, because patients correctly predicted that both treatments would be effective.

The authors overstated the statistically insignificant difference in ratings on the SAD (seasonal affective disorder) Supplementary Items at baseline and during midday light therapy by giving it equal weight with statistically significant differences. Also, they appear to have used 15 too many degrees of freedom in their paired t tests (or else they inappropriately did independent comparisons). In conclusion, given the lack of knowledge about phrase-related curves in humans and the inappropriate choice of the midday light comparison, Dr. Jacobsen and associates are in no position to conclude that the modest antidepressant effects of their light treatments were not likely to have been due to a phase shift of circadian rhythms, particularly since they have not measured circadian phase shifts. We also doubt just how good an antidepressant bright midday light is, considering that light many times brighter than 2500 lux is available outdoors year-round. One of the reasons that our phase-shift hypothesis is interesting is that it explains winter depression in the context of a seasonal change in environmental light, that is, the later occurrence of dawn in the winter.

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Dr. Jacobsen and Associates Reply

SIR: We did not claim that our finding refuted the theory of Drs. Lewy and Sack, just that it was not consistent with that theory—a conclusion by which we stand. Psychiatric theories are notoriously difficult to refute, and this is especially so with the phase-shift theory, which has undergone mutations to account for conflicting data. For example, a recent version (1) takes into account both phase-shifting and "activating" effects of light. The latter mechanism, introduced to account for the efficacy of evening light for seasonal affective disorder, which should have aggravated winter depressive symptoms according to the original version of the theory (2), could just as easily account for the efficacy of midday light that we observed. We should note that the efficacy of midday light in seasonal affective disorder has been confirmed by another research group (3).

Although our study argues against phase shift as a critical mechanism in the antidepressant effects of light in seasonal affective disorder, it is by no means definitive. Points about the limitations of the study, many of which we described in the original discussions and others of which have been elaborated upon by Drs. Lewy and Sack, are well-taken. Expectations and placebo effects remain a problem, and the possibility of a type II error cannot be eliminated. Other criticisms seem less valid. The raters were blind. Mean±SD withdrawal Hamilton depression scale scores following the first and second weeks of treatment were 20.2±5.7 and 20.2±7.2, respectively, suggesting that there was no ordering effect. Exposure to sunlight on the way to work was much the same during treatment and baseline weeks, suggesting that this was not the active principle. Although Drs. Lewy and Sack note that the sun often shines at midday in winter, in our experience people are often in the dark during the day, either as a result of cloud cover or because they do not go outdoors. A valid central question is why the patients of Drs. Lewy and Sack responded better to morning light than ours did. One possibility is that our patients were more depressed at baseline; they had a mean Hamilton depression rating of 22.4. In the study by Dr. Lewy et al. (2), the baseline rating was 15.4. The mean decrease in Hamilton scores in our study (6.1 points) was not much less than the 8.8 mean decrease reported by Drs. Lewy and Sack.

Drs. Lewy and Sack and their group have made valuable contributions to our understanding of phototherapy for seasonal affective disorder by pointing out that time of day may

be important in determining efficacy. Their phase-shift theory of light's mechanism of action is interesting and may be viable, at least in certain cases. However, data that argue against the theory should be taken seriously and not simply dismissed on methodological grounds. As Drs. Lewy and Sack and their colleagues have acknowledged (2), there may be alternative explanations for circadian differences in the efficacy of phototherapy. At this time it seems reasonable to say that although most researchers and clinicians agree that bright light is helpful for the winter symptoms of seasonal affective disorder, the mechanism of action remains unknown.

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Premenstrual Exacerbation of Binge Eating in Bulimia

SIR: The positive findings reported in the article by Madeline M. Gladis, M.A., and B. Timothy Walsh, M.D., on premenstrual exacerbation of binge eating in bulimia (1) contrast with our negative findings, reported in a previously published study (2), with respect to the relationship between binge eating and the premenstruum. We would like to point out that the authors' incomplete reporting of the statistical analyses and data of our study misrepresented the procedures we used, with resulting negative implications about the robustness of our methodology.

A crucial point in their discussion was that "the more important indicator of menstrually related effects is the change relative to an individual's own average from one phase to the next" (1, p. 1594). However, they did not mention that this is precisely the analysis we conducted; in our study, the assessment of an association between the premenstruum and an exacerbation of binge eating and other problem eating behaviors was based primarily on calculations of change scores comparing the premenstrual to the intermenstrual phase. Instead, Ms. Gladis and Dr. Walsh criticized the fact that we also presented correlations demonstrating strong relationships between problem eating behaviors over different phases of the menstrual cycle. However, a reading of their article leaves the impression that we only conducted correlational analyses and did not conduct the crucial change score analyses. This point is extremely important in comparing the data of each of the studies.

Ms. Gladis and Dr. Walsh also questioned our findings because 44.4% of the 45 subjects were taking either antidepressants or tranquilizers during our study. However, the majority of our volunteer bulimic subjects who were taking medications were not on a controlled medical regimen. We indeed reported that there were no significant differences in use of medication between the groups which exhibited a premenstrual exacerbation of mood and those which did not and that further statistical evaluations failed to demonstrate differential use of medication at different phases of the menstrual cycle. While we concede the possibility that for some subjects medications might have altered premenstrual binge eating, there is a trade-off between evaluating a large-enough number of subjects so that statistical analyses are meaningful and using highly stringent selection criteria and a markedly lower number of subjects (there were 15 in the Gladis and Walsh study) at the expense of a loss in statistical power.

We are puzzled by the conclusions drawn by Ms. Gladis and Dr. Walsh. They conducted two types of analysis of variance procedures with subsequent comparisons of means to assess frequency of binge eating at different phases of the menstrual cycle. While the numerical value of the mean binge frequency was higher for the 5-day premenstrual phase in their study, the subsequent comparisons of means consistently demonstrated that there were no statistically significant differences in mean binge scores between the 5-day premenstrual segment and both the 5–10 days before menses and the 5-day menstrual segments. It is unclear why Ms. Gladis and Dr. Walsh referred to a 15-day segment of the menstrual cycle in which individual segments were not significantly different from one another in mean binge frequency as a premenstrual exacerbation of binge eating.

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Ms. Gladis and Dr. Walsh Reply

SIR: Because of the uncertainties about how best to assess menstrually related phenomena, we are pleased to have the opportunity to discuss the methodologies used in our recent study and in the study by Dr. Leon and associates.

In our paper we expressed concern that Dr. Leon and her colleagues "partly based their conclusion" on a correlational analysis which is relatively insensitive to changes within individuals across the menstrual cycle. In their letter, Dr. Leon and associates do not disagree with our concern but object to our focusing on the correlational analysis. We believe our attention reflects their own emphasis. In their paper they noted that "one of the most striking findings" was the "degree of stability in binging . . . across the menstrual cycle." This statement was immediately followed by the results of the correlational analysis, which were then presented in a table. Thus, we feel our focus on this analysis was entirely appropriate.

In their letter, Dr. Leon and colleagues note that they performed an additional analysis of change scores. The major focus of this analysis was a comparison of the changes in eating behavior in a group of eight women categorized as having a "premenstrual pattern" of emotional and physical symptoms with the changes in a group of 37 women without

such a pattern. No difference between the groups was detected. This method appears to test whether there is a relationship between changes in eating behavior and a premenstrual pattern. Changes in eating behavior related to the menstrual cycle but unrelated to the premenstrual pattern of physical and emotional changes would not be identified by this method.

In one sentence, Dr. Leon and her associates indicated that there was no evidence of changes across the menstrual cycle in eating-related symptoms in either the group with or the group without the "premenstrual pattern." No statistics were presented, and there was no indication that an analysis of the combined sample was conducted. Thus, we continue to feel that there were major differences in the methods used by those authors and ourselves and that these differences, along with several others we noted in our paper, may account for the different results of the two studies.

Dr. Leon and colleagues agree with our concerns about the inclusion in their study of patients who were taking medication. Conversely, we share their concern about the small number of patients in our study. Nonetheless, the two methods of analysis we used had sufficient statistical power to detect a significant change in binge frequency over the menstrual cycle.

Finally, Dr. Leon and associates express puzzlement over our labeling our results as a "premenstrual exacerbation of binge eating." Since the index of binge frequency was higher in the premenstrual segment than in any of the other six segments of the menstrual cycle, it did not seem inappropriate to describe the results as a premenstrual exacerbation. Nonetheless, we agree that additional data are necessary to confirm our interpretation of these initial findings.

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Effect of Bromocriptine in Hyperprolactinemia

SIR: The article by Michele C.S. Koppelman, M.D., and associates (1) provided an important confirmation of previously published findings (2–5) on the presence of psychological distress in hyperprolactinemic women and the effectiveness of bromocriptine in ameliorating such distress. Unfortunately, however, the authors misrepresented the previous literature.

First, they criticized the first controlled study on the psychosomatic aspects of hyperprolactinemic amenorrhea (2) on the grounds that it had an inadequate control group (healthy hospital employees). The choice, they suggested, "was a poor one because of the psychological stress related to hospitalization." Dr. Koppelman and associates, however, forgot to mention that there was a second control group in the study (normoprolactinemic women with secondary amenorrhea) in which these factors were controlled for. They also failed to mention that the results of this first study, performed in Italy, were replicated by a second controlled study performed in the United States (3), where three more control groups (psychiatric outpatients, family practice patients, and employees) were available. On the basis of their six patients, Dr. Koppelman and colleagues concluded that depressive symptoms in hyperprolactinemia are mild and that the previously reported findings of greater hostility (2, 3) were probably spurious (inadequate control groups?). Again, other independent investigations confirming the results of our group (6) were not cited. Further, a study (4) where one-third of 18 hyperprolactinemic women were found to suffer from a major depressive episode according to the Research Diagnostic Criteria was not mentioned. Finally, Dr. Koppelman and associates did not use a sensitive self-rating scale for assessing hostility, such as the Symptom Questionnaire that was used in previous studies (2–4).

Dr. Koppelman and associates disregarded a published crossover controlled study of bromocriptine in hyperprolactinemia (5) because "data were tabulated at a single point at the end of each 6-week interval," even though the procedure was justified by the fact that a certain lag period is required for organic affective syndromes to remit upon appropriate endocrine treatment (6).

I feel that Dr. Koppelman and colleagues should show more awareness of the very small sample size of their study. Hyperprolactinemic women may suffer from mild symptoms of depression. However, in some cases such depression may reach melancholic proportions and involve considerable risk of suicide (6). Treatment with bromocriptine should be promptly provided (5). The syndrome of depression, hostility, and anxiety in a woman complaining of amenorrhea, especially if associated with decrease of libido and galactorrhea, should lead to the suspicion of hyperprolactinemia. Clinicians in general, and psychiatrists in particular, should not underestimate the psychiatric consequences of hyperprolactinemia in women (6).

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Dr. Koppelman and Colleagues Reply

SIR: It is unfortunate that Dr. Fava took umbrage at our discussion of his previous studies. We certainly acknowledge the important pioneering contributions of Dr. Fava and his associates to the understanding of the psychological attributes of hyperprolactinemia. The normoprolactinemic control group in his first study (1) did partially control for the stress of hospitalization but only served to show that hyperprolactinemic women may become more hostile than normoprolactinemic amenorrheic women in response to the stress of hospitalization, not that they are generally more hostile than these or other women under usual circumstances.

Dr. Fava states that we failed to cite "other independent investigations confirming the results of our group," yet his

citation for this statement is a review article which was published after our article was published. We did cite the controlled study by Kellner et al. (2) confirming the results of Dr. Fava and co-workers' study in Italy but did not elaborate on the findings. The other paper by Dr. Fava and his colleagues (3) was not cited because we were unaware of its existence.

We never stated or implied that the previous reports of hostility in hyperprolactinemic women were "spurious." We only stated that we did not find hostility among our subjects, and we elaborated features of our study group and those in previous reports that might have accounted for the different observations. We disagree with Dr. Fava's assertion that we "did not use a sensitive self-rating scale for assessing hostility." The Profile of Mood States (4) is considered to be a sensitive, well-validated rating scale that does assess anger-hostility.

We did not "disregard a published crossover controlled study of bromocriptine in hyperprolactinemia" (5). We acknowledged it and pointed out the several ways in which the study design differed from ours.

We feel that our study had unique aspects that were not addressed by the earlier studies. Our patients and control subjects were matched closely on eight factors influencing life style to control variables of marital status and duration, children at home, fertility potential, and employment. Our patients had a mean duration of documented hyperprolactinemia of 4.6 years, so as to exclude the anxiety associated with a recent diagnosis and evaluation. Structured interviews were conducted by observers who were unaware of the subjects' endocrine status, so as to exclude potential observer bias. We evaluated libido by means of patients' daily self-reports of sexual events. We feel that our study is an important contribution to the understanding of the psychological effects of hyperprolactinemia, both in confirming earlier observations made by using a different experimental design and in expanding the observations on libido in hyperprolactinemia in a new direction.

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Aims of Therapy and Research

SIR: Norman E. Zinberg, M.D., in his article on the private therapeutic interview (1), referred to "Sigmund Freud's view that therapeutic and research aims are antithetical" in the context of discussing the "therapist's ability to fulfill the therapeutic task while serving as a formal researcher." Dr. Zinberg based his claim on Freud's paper "Recommendations to Physicians Practising Psycho-Analysis" (2). Considering that Freud himself accomplished quite a bit of scientific research while functioning as a therapist, it appears that Dr. Zinberg's statement warrants further clarification.

Freud actually asserted that "one of the claims of psychoanalysis to distinction is, no doubt, that in its execution research and treatment coincide" (2). Here, in fact, the pure scientific aim of knowing and the therapeutic aim of healing do indeed converge. Psychoanalysis is unique in this respect. What Freud warned against, however, was the earmarking of analytic cases for specific research purposes from the beginning of treatment, because this would result in intrusive attempts at premature synthesis and prediction. He advocated instead that the analyst proceed with open-mindedness, freedom from presuppositions, and a willingness to be surprised. He suggested that a comprehensive synthesis of case material be attempted only after an analysis has been completed. In essence, Freud implied that it would be both bad therapy and bad science to impose theoretical expectations on an analysis. He generally considered research and treatment in psychoanalysis to be mutually dependent rather than antithetical, despite acknowledging that, after a certain point in an analysis, the techniques required for research and treatment would come to oppose each other. His own case studies, of course, offer unequivocal examples of their productive interrelationship.

Last, I will risk pointing out the obvious by noting that Freud's comments concerned only strict psychoanalysis, as opposed to other types of psychotherapy. To the extent that formal research is defined narrowly as necessitating breaches of privacy or distortion of material, then it is indeed a hindrance to treatment, but in the broader sense, formal psychoanalytic research proceeds quite effectively as part and parcel of the therapeutic process.

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Dr. Zinberg Replies

SIR: Dr. Garcia raises a number of interesting issues—really, too many to be answered in a letter. The question of the extent of the difference between psychotherapy and psychoanalysis would in itself fill this entire issue of the *Journal* at the very least. Suffice it to say that I think there is research and there is research. It is my impression that what Dr. Garcia means in his quotations of Freud's comments is that, in thinking about the nature of the interaction with the patient and what goes on in the therapy, the study of the situation can be, at its best, research. I have the impression that Dr. Garcia is not thinking of research as the actual intrusion of an imposed research methodology, including observation of the process. In the former idea of research, while there are

certain personal issues having to do with where the therapist's attention is directed, this seems to be a different kind of intrusion from the intrusion caused by a mechanical device. I find it important to reiterate something that is at least implicit in my article, which is that I am entirely in favor of all sorts of research on the psychotherapeutic or psychoanalytic situation. My contention is only that research may well change the situation and that what one ends up studying is not identical to the situation without the research. This may well apply to both kinds of research, but more certainly to the latter.

I am reminded of Goffman's comment that "generally, behavioral and social research by its very nature has a potentially intrusive quality. At the microlevel, it is a form of social interaction that often tries to elicit private information or observe unguarded behavior. At the macrolevel, it contributes to expanding the areas of human activity that are exposed to public scrutiny" (1). However, both of these levels of research are justifiable and to a certain extent "positive in their impact," yet they "lend an element of ambiguity to social research as a social process" that must be kept in mind.

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Axis IV of *DSM-III*

SIR: We read with interest the article "*DSM-III* Axis IV Revisited" by Joseph M. Rey, Ph.D., F.R.A.N.Z.C.P., and associates (1). The problem with "revisiting" axis IV is that few investigators have "visited" yet for the first time. The reliability studies reviewed in the article came from only four research groups, three of which reported findings only for children and adolescents. The validity studies appear to have been limited to five groups, and one of these (2), as the authors pointed out, did not actually use axis IV in the manner intended by *DSM-III*.

The argument that the problems encountered in making axis IV ratings for children and adolescents are likely to be the same as those for other age groups is unconvincing in the absence of more data. We have preliminary results on adults that corroborate some of the authors' findings and conclusions but not others. Like Dr. Rey and his associates, we found that relatively severe stressors were more likely to be independently elicited by two raters than were mild stressors and that the overall severity rating on axis IV was determined by the most severe stressor when more than one stressor was listed. In contrast to the experiences of Dr. Rey and colleagues, however, we found that actual events listed on axis IV correlated almost as highly ($r=0.72$) as did the examples given for the *DSM-III* scale ($r=0.80$) with an independent severity system derived for the Psychiatric Epidemiology Research Interview Life Events Scale (3). This suggests that clinicians can assign meaningful severity ratings to stressors that are not among the *DSM-III* examples.

What is needed are more reliability studies that include various groups of patients and clinicians who have diverse levels of experience. A study of axis IV reliability following an intensive training program for raters in the use of the multiaxial system would indicate how much reliability could be improved. The reliability of any instrument will vary with the patients and clinicians involved, as well as with the characteristics of the instrument itself.

Each of the conventions for the use of axis IV should be evaluated as a potential source of unreliability and for its effect on validity. Schrader et al. (4) found that the *DSM-III* requirement that the stressors be etiologically related to the current mental disorder necessitated difficult judgments, and therefore they ignored this convention. Their data showed, nevertheless, the expected associations between axes I and IV; for example, among patients with psychotic disorders, those with psychotic affective disorders were judged to have experienced more stress than those with nonaffective psychoses. In our experience, the relevance judgment accounts for numerous differences between axis IV assessments and those yielded by a standardized life events instrument.

With respect to predictive validity, Zimmerman et al. (5) recently failed to find the predicted relationship between high severity ratings on axis IV and good prognosis in a sample of depressed inpatients. Other studies of the usefulness of axis IV for planning treatment or judging prognosis should be done using homogeneous groups of patients with psychotic anxiety, somatoform, or personality disorders.

Some of those who worked on the revision of *DSM-III* believed that the scanty research that had been generated by *DSM-III*'s multiaxial system was evidence enough for an overhaul (6). The changes introduced in *DSM-III-R* may stimulate more research or may make it more difficult to synthesize a body of empirical data. It is likely that future changes in the classification will require empirical support rather than be motivated by its absence.

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Dr. Rey and Colleagues Reply

SIR: We thank Drs. Skodol and Shrout for updating our review of *DSM-III* axis IV with more recent material, and we await with interest the publication of their results. Many of the points we made briefly in the review have been argued at greater length elsewhere (1–4). It was a pleasant surprise to discover that, for once, the literature on children and adolescents which was available for review was both more in-

formative and more extensive than the literature on adults. No doubt the research vacuum on this topic in adult psychiatry between the publication of *DSM-III* and that of *DSM-III-R* is something of an embarrassment, but we make no apology for generalizing from child/adolescent data to adults in the absence of specific material, if only because we believe that our colleagues in child psychiatry will find the reversal of the usual process a refreshing change.

A perusal of our previous papers (1–4) will demonstrate that we have no serious dispute with Drs. Skodol and Shrout about the need for diversity of all kinds in reliability and validity studies. The more specific issues they raise can only be addressed by data. We have so far found no improvement in axis IV reliability in a series of adolescents, which has now reached 393 in number, who have been diagnosed by two, three, or four very experienced judges. Reliability for other axes is higher. We attribute this to the definitions in axis IV rather than to our judges, our patients, or our procedures. Our rating study of 77 stressors (2) would provide a basis for exploring the association reported by Drs. Skodol and Shrout between the ratings assigned to individual events listed in axis IV and external scalings. However, in a previous look at this possibility (3), we found that it was necessary to make a further judgment in order to decide which "generic" stressor from the consensus list should be matched to the specific stressor listed by a judge; however this is done, the association between the specific opinions of judges and ratings on the external scale will depend on how multiple observations of particular stressors are treated in the analysis. Our conclusion that individual judges are unreliable in assigning ratings to specific events does not preclude their average ratings correlating highly with those on an external scale (2); the point is that the ratings vary considerably from one judge to the next.

Finally, we are of the opinion that the hurried changes to axis IV and also to other parts of *DSM-III-R* may simply confuse clinicians and inhibit research (5).

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Lorazepam: Therapeutic for Catatonic Schizophrenia?

SIR: In "Lorazepam for Psychogenic Catatonia" (1), Sultana A. Salam, M.D., and associates indicated that intramuscular lorazepam can be used for therapeutic purposes in catatonic schizophrenia (case 3). The use of diazepam (2) and a short-acting barbiturate (3, 4) has been described for diagnostic purposes and short-term emergency management, but "however spectacular the immediate results seem to be, the technique has no significant therapeutic value" (4), as the results are not sustained in the absence of treatment with neuroleptics.

Even in the case described by Dr. Salam and colleagues, the patient was prescribed 20 mg/day of haloperidol "because of persistent delusions of control," so it cannot be concluded that lorazepam alone was therapeutic in this case. In this context, it is worth noting that in the other two cases reported, the patients who responded to lorazepam alone had diagnoses of conversion disorder with inhibited sexual excitement and adjustment disorder with depressed mood (initial diagnosis: conversion disorder), respectively.

I suggest that the retarded catatonia seen in major depressive disorder, catatonic schizophrenia, and periodic catatonia requires treatment of the underlying disorder (e.g., with antidepressants, ECT, neuroleptics, lithium, T_3) and that the use of parenteral benzodiazepines or short-acting barbiturates is only for diagnostic purposes and short-term emergency management. However, these psychopharmacological agents may be therapeutic in the retarded catatonia seen in conversion disorder.

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Dr. Salam and Associates Reply

SIR: Dr. Ahuja questions the use of the term "therapeutic" to describe the action of intramuscular lorazepam in the treatment of catatonic schizophrenia. He feels that this was incorrect, since lorazepam alone was not therapeutic and the underlying disorder required haloperidol. I believe Dr. Ahuja has missed the point; we never claimed that lorazepam alone was therapeutic for catatonic schizophrenia. We emphasized that lorazepam is therapeutic for catatonic *states* and/or symptoms regardless of the underlying etiology and that it alleviates the symptoms of stuporous catatonia, such as mutism, posturing, waxy flexibility, rigidity, and refusal to eat and ambulate. The benefits of lorazepam in catatonic schizophrenia are analogous to those of furosemide in congestive heart failure; i.e., furosemide treats symptoms of congestive heart failure, such as fluid overload, not the cardiac failure itself. We definitely agree with Dr. Ahuja that the underlying cause of catatonia should be treated properly.

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Need for Differential Therapeutics

SIR: Separate letters to the Editor by Arnold L. Lieber, M.D. (1) and Breck Lebegue, M.D. (2) bring to one's attention the importance of differential therapeutics in psychiatry.

I was most impressed with Dr. Lieber's fortitude in developing, by trial and error, an extensive medication program for the treatment of rapid cycling bipolar patients. However, he did not describe how the patients were selected, except for the fact that they had rapid mood swings. He developed an extensive regimen involving four or five different medications, all of which individually have the risk of toxicity but in combination would be highly likely to cause drug interaction. As he pointed out correctly, this sort of regimen should only be attempted in an inpatient setting. Unfortunately, Dr. Lieber did not describe what sort of medical diagnostic evaluation was undertaken before patients were started on this program.

Similarly, Dr. Lebegue described mania precipitated by fluoxetine and, in passing, mentioned that the first patient's "TSH concentration was slightly elevated." The patient was treated with lithium and apparently was later changed to fluoxetine, resulting in a switch to mania. Interestingly, the slightly elevated TSH concentration was ignored and, apparently, no further attempt was made to investigate the cause of this.

In my experience, I have found large numbers of patients who have underlying medical problems that contribute to rapid cycling bipolar disorder or other affective disorder which fails to respond to standard treatments. This is substantiated in the literature. For example, Black et al. (3) reviewed the cases of more than 1,000 patients, comparing the outcome in the treatment of primary versus secondary depression. They found that patients with secondary depression were much less likely to respond to typical adequate treatment than patients with primary depression.

Both letters to the Editor lacked detailed descriptions of the medical evaluations that preceded psychotropic drug treatment. There was, in both cases, a need for evaluation of thyroid function. Although Dr. Lieber obviously feels that thyroid hormone plays an important role in mood stabilization, he did not describe routinely obtaining thyroid-releasing hormone (TRH) stimulation tests for the patients he treated. Similarly, Dr. Lebegue indicated that one of his patients had a slightly elevated thyroid-stimulating hormone (TSH) level, but this was not further pursued by evaluation of TRH stimulation of TSH. There is a good possibility that, in the first case presented by Dr. Lebegue, the patient might have responded to lithium carbonate if thyroid hormone had been given. It is not clear whether fluoxetine was added to lithium or lithium was first stopped and fluoxetine instituted. In either case, it would have been most informative to obtain the results of a TRH stimulation test to determine whether addition of thyroid hormone was indicated.

Once again, it is evident that there is a tendency in psychiatry to ignore the underlying medical condition of the patient and proceed with treatment without taking into account contributing medical factors. Although Dr. Lieber's and Dr. Lebegue's letters were very interesting, they failed to describe pretreatment medical evaluation of a depth sufficient to facilitate diagnosis and treatment. I strongly believe that medication treatment in psychiatry should be predicated on a specific diagnosis and a careful understanding of the patient's physical, psychological, and social conditions.

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Dr. Lieber Replies

SIR: Dr. Zarr's critique affords the opportunity to describe the clinical evaluation of our rapid cycling bipolar patients. Our hospital admits patients whose affective illness interferes with work, family, or social functioning. Biopsychiatric assessment includes a complete psychiatric and medical history, family psychiatric history, automated symptom inventory and depression self-rating scales, physical and neurological examinations, and laboratory assessment, including CBC, urinalysis, RPR, BCP-17, chest X-ray, ECG, dexamethasone suppression test, TRH stimulation test, and quantitative EEG. A diagnosis of rapid cycling bipolar disorder requires either a history of four or more episodes within a year or personal observation of at least three switches between irritable hypomania and depression during the initial week of hospitalization.

Upon reviewing the records of seven such patients treated during the past year, I found the following. The patients were all women over the age of 30, none of whom had preexisting or current medical conditions, except for one with mild hypertension. Three had an augmented TSH response to TRH (ΔTSH>20 μU/ml) and one had a blunted response (ΔTSH<5 μU/ml). For these four patients, the free T_3 index, the free T_4 index, and thyroid antibodies were normal. A diagnosis of subclinical hypothyroidism in the three patients with augmented TSH responses is arguable. Most endocrinologists disagree with this concept and feel that the finding of enhanced or augmented ΔTSH alone has no clinical significance. Nonetheless, these patients do not respond to the method of treating rapid cycling bipolar illness described in my letter unless a small dose of L-thyroxine (0.1 mg/day) is included. A colleague and I have previously proposed (1) that the augmented TSH response to TRH in a depressed patient with otherwise normal thyroid indices may represent a trait marker for bipolar disorder. Other authors (2, 3) have considered this possibility. Confirmation awaits further independent replications.

Dr. Zarr points out the risk of possible adverse interactions with the drug combination I suggest. This has not occurred in any of our patients thus far. The doses we use are lower than those recommended for each drug when used alone. Caution must be exercised when adding other drugs, however. I am in full agreement with Dr. Zarr's final sentence; accurate diagnosis in psychiatry is the sine qua non of successful pharmacotherapy.

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ARNOLD L. LIEBER, M.D.
Miami Beach, Fla.

Psychotherapy Practice and Reimbursement

SIR: I am writing as a psychologist on the faculty of a medical school and as one who enjoys his collegial relationships with psychiatrists and regularly refers patients to them. In his commentary "Effects of the New Economic Climate on Psychotherapeutic Practice" (1), Paul Chodoff, M.D., stated, "These are not the best of times for psychoanalysis and medical psychotherapy." His position is akin to that of Lee Iacocca bemoaning the fact that these are troubled times for American-made cars. However, unlike Mr. Iacocca, Dr. Chodoff suggested that his product be selectively protected in the marketplace by means of a special subsidy—third-party reimbursement—not available to other practitioners. (On second thought, perhaps that is exactly what the government loan to Chrysler was!)

I believe that Dr. Chodoff's commentary falters because of its primary assumption: the mixed metaphor "medical psychotherapy." The bailiwick for biomedical treatment of mental disorders (e.g., psychopharmacological treatments, ECT) is uniquely that of the psychiatric discipline. However, psychotherapy is essentially a communicative art, an educational endeavor, and, as Szasz (2) put it, "a method of personal influence." There is nothing intrinsic to psychiatric residency training that makes the generic psychiatrist uniquely qualified, in relation to other mental health professionals, to use this method of therapy. It is essential not to confuse biomedical practice with an educational method of healing that is cost-effective and enhances personal health (3).

What is especially problematic is Dr. Chodoff's failure to mention two important psychotherapeutic developments in the treatment of mental disorders: family psychotherapy and strategic psychotherapy (e.g., adaptations of the work of Milton Erickson, M.D.). There has been considerable documentation of the efficacy and cost-effectiveness of both modalities (3, 4) in comparison with the traditional medical psychotherapy described by Dr. Chodoff. I hope that his position does not represent the sort of reactionary attitude that Freud faced when he presented a revolutionary new treatment for hysteria to the Viennese medical community.

It seems that Dr. Chodoff takes what he already perceives to be an "uneasy and ambiguous" relationship and asks to transform it into an open conflict. I do not begrudge my psychiatrist colleagues their biomedical expertise; I greatly appreciate it in our work together. I, unlike Dr. Chodoff, would not suggest that psychiatrists *not* be reimbursed identically to myself for the practice of "a method of influencing others," although this practice is derived from an academic discipline—psychology. I have every reason to believe that psychiatrists can master this nonbiomedical discipline and its advances just as well as other mental health professionals whom I consider colleagues do. And I believe psychiatrists deserve comparable reimbursement!

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JAMES M. SCHIFFNER, PH.D.
Buffalo, N.Y.

Dr. Chodoff Replies

SIR: Dr. Schiffner has a point when he refers to "medical psychotherapy" as a mixed metaphor. However, he is quite wrong when he states that psychotherapy is "a method of influencing others" which is "derived from an academic discipline—psychology." Physicians were helping patients by means of words and nonverbal communication for centuries before they could do very much else for them and long before academic psychology was dreamed of. Further, the theoretical mentor of most psychiatrists (and many psychologists) was a physician, Sigmund Freud. But Dr. Schiffner is right in pointing out the conceptual confusion over "medical psychotherapy," a term often used more in a rhetorical than a precise sense.

There is a real problem about the definition of individuals treated with psychotherapy. Are they "patients" or "clients"? Physicians treat the former, not the latter. However, the distinction has become blurred, and it is my contention that this blurring is responsible for some of the difficulties psychiatrists are having with third-party payers who are guided by a version of the medical model in making their payment decisions. Thus, to my mind, medical psychotherapy, if it means anything, means psychotherapeutic treatment of medical patients by physicians, usually those trained in psychiatry. If psychiatrists want to be paid by third parties for this practice, they will have to establish the medical nature of their patients' problems. The other choice for psychiatrists is to accept the fact that some of the people they treat do not meet medical criteria. Psychiatrists will then be seeing both clients and patients, and psychiatrists' differences from nonmedical therapists will be attenuated, possibly to the point where third-party payment under the medical model will be threatened. I believe that this is an important issue for psychiatrists. Medical psychotherapy needs to be more than a shibboleth; its meaning and usefulness need to be debated and defined by psychiatrists.

PAUL CHODOFF, M.D.
Washington, D.C.

Neuropsychiatry as a Subspecialty of Psychiatry

SIR: Joel Yager, M.D., and Donald G. Langsley, M.D., recently described forces favoring subspecialization in psychiatry and listed a number of potential psychiatric subspecialties (1). Notably, they left our neuropsychiatry, giving only brief mention to "behavioral neurology," which is somewhat different. Neuropsychiatry, the specialty concerned with the treatment of psychiatric complications of neurological disease and the assessment of behavioral disor-

ders from an integrated psychiatric and neurological perspective, has good claim to a specific body of knowledge and skill essential to its practice. The neuropsychiatrist must be competent in all those areas of clinical neurology relevant to the diagnosis and management of neurobehavioral disorders, including the neurological examination, the interpretation of neurodiagnostic tests, and the management of the neurological disorders underlying the behavioral disorders treated.

A psychiatrist's acquisition of this knowledge and skill almost always requires 1) residency training in neurology as well as psychiatry, 2) the completion of a fellowship program with extensive supervised neurological experience, or 3) extensive work as a psychiatrist on a multidisciplinary team that includes a neurologist. To us, it seems quite unlikely that any psychiatrist could become a competent neuropsychiatrist without additional formal training. Many of the other psychiatric subspecialties reviewed by Drs. Yager and Langsley are presently practiced by individuals who have learned their skills on the job. While we would not dispute that formal fellowship training may be valuable for all of these potential subspecialties, it may not be essential to most of them in the same way that neurological training is to the neuropsychiatrist. If the reason for labeling and certifying the practice of a subspecialty is to identify those qualified to practice it, neuropsychiatry would certainly warrant subspecialty status.

As we have mentioned, we contend that there is a distinction between neuropsychiatry and behavioral neurology. Behavioral neurology, a neurological subspecialty, does not require formal psychiatric training and presently is focused on intracerebral determinants of behavior, to the relative exclusion of developmental, psychological, and social factors. In contrast, neuropsychiatry attempts to integrate behavioral neurology with the perspective of clinical psychiatry. We believe that individuals who have received multidisciplinary training are best able to evaluate and treat complex or refractory neuropsychiatric problems and to provide consultations to generalists with regard to neuropsychiatric problems encountered in general psychiatric and neurological practice.

REFERENCE

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BARRY S. FOGEL, M.D.
RANDOLPH SCHIFFER, M.D.
Rochester, N.Y.

Drs. Yager and Langsley Reply

SIR: The letter by Drs. Fogel and Schiffer regarding neuropsychiatry as a potentially new subspecialty of general psychiatry is a welcome validation of our perceptions of the field. We suspect that we neglected to mention several other potential areas of subspecialization as well, simply because it is almost impossible to know all the diverse areas into which the field is moving and which of them will, in fact, achieve the status and momentum necessary for recognition as a subspecialty. With the publication of a major textbook and the start of a subspecialty journal, neuropsychiatry may be beginning the process; also necessary are societies, fellowships, a growing research base, demonstration of a distinct body of knowledge and technical skills not possessed by generalists, demonstration of an unmet clinical need that can financially sustain the subspecialty, and all the other scientific and political prerequisites of subspecialty status. Neuropsychiatry, and other areas as well, are off and running. Which of them will ultimately leap all the hurdles remains to be seen.

JOEL YAGER, M.D.
Los Angeles, Calif.
DONALD G. LANGSLEY, M.D.
Evanston, Ill.

Reprints of letters to the Editor are not available.

1987–1988 Annual Report of the American Board of Psychiatry and Neurology, Inc.

Composition of the Board

At its business meeting on Nov. 15, 1987, the American Board of Psychiatry and Neurology (ABPN) elected the following officers, who began their terms on Jan. 1, 1988: Dr. Robert Michels, President; Dr. Jack P. Whisnant, Vice-President; Dr. Elliott L. Mancall, Secretary; Dr. Maurice J. Martin, Treasurer; and Dr. Layton McCurdy, Executive Committee Member-at-Large.

Dr. Lenore C. Terr (San Francisco), nominated by the American Psychiatric Association, was elected to a 4-year term on the Board to succeed Dr. John A. Talbott, who completed his second 4-year term on Dec. 31, 1987. Dr. Maurice J. Martin (psychiatrist), nominated by the American Medical Association, and Dr. William E. Bell (child neurologist), nominated by the American Neurological Association, were renominated and reelected to serve second 4-year terms as Directors. The names of the 1988 ABPN Directors follow; those serving second 4-year terms are not eligible for reelection.

Nominated by the American Medical Association: Dr. Maurice J. Martin (second term expires Dec. 31, 1991), Dr. John F. McDermott, Jr. (second term expires Dec. 31, 1990), and Dr. William L. Webb, Jr. (second term expires Dec. 31, 1989).

Nominated by the American Psychiatric Association: Dr. Layton McCurdy (second term expires Dec. 31, 1990), Dr. Robert Michels (second term expires Dec. 31, 1989), Dr. James H. Shore, M.D. (first term expires Dec. 31, 1990), Dr. Lenore C. Terr (first term expires Dec. 31, 1991), and Dr. Gary J. Tucker (first term expires Dec. 31, 1988).

Nominated by the American Neurological Association: Dr. William E. Bell (second term expires Dec. 31, 1991), Dr. J. Donald Easton (first term expires Dec. 31, 1988), Dr. Ludwig Gutmann (first term expires Dec. 31, 1990), and Dr. Stuart A Schneck (first term expires Dec. 31, 1989).

Nominated by the American Academy of Neurology: Dr. Robert A. Fishman (second term expires Dec. 31, 1988), Dr. Elliott L. Mancall (second term expires Dec. 31, 1990), Dr. N. Paul Rosman (second term expires Dec. 31, 1990), and Dr. Jack P. Whisnant (second term expires Dec. 31, 1990).

Dr. Stephen C. Scheiber is the Executive Secretary of the ABPN.

Examinations

Part I. At the part I (written) examination on April 12, 1988, 1,787 psychiatrists were examined; 1,079 (60.4%) passed and 708 (39.6%) failed. A total of 684 neurologists (including child neurologists) were examined; 349 (51.0%) passed and 335 (49.0%) failed. Table 1 contains the numbers of candidates in each year from 1983 to 1988. The next part I examination will be held on April 4, 1989. Applications for that examination are due no later than Sept. 1, 1988, and are available from the Board office (new address and telephone number given in item 5 of following section).

Part II. At the 1987 part II (oral) examinations held in Houston (Jan. 11–13), Los Angeles (April 26–28), and New York (Nov. 15–17), 1,403 psychiatrists, 419 neurologists, and 60 child neurologists were examined. For statistics on these examinations, see table

TABLE 1. Candidates for ABPN Part I (Written) Examination, 1983–1988

	Number of Candidates					
Physician Status	1983	1984	1985	1986	1987	1988
Met requirements	2,187	2,029	2,506	2,703	2,649	2,861
Accepted examination	2,064	1,929	2,409	2,574	2,477	2,782
Appeared for examination	1,849	1,738	2,167	2,301	2,255	2,471

2. The examination sites for 1988 are San Francisco (March 6–8), Kansas City, Mo. (June 12–14), and Chicago (Oct. 16–18).

Board Decisions and Items of Interest

1. The ABPN reaffirmed its policy that, beginning July 1, 1988, any osteopathic physician entering a postgraduate year 2 program must have successfully completed a postgraduate year 1 program approved by the Accreditation Council for Graduate Medical Education, as described in the ABPN "Information for Applicants" pamphlet, which is available from the Board office. In addition, an applicant seeking certification in both psychiatry and neurology who begins postgraduate training after July 1, 1987, must complete a postgraduate year 1 program that meets the requirements for entry into a neurology program.

2. The ABPN reaffirmed its policy whereby all licensing and training requirements must be met before application for examination, except for residents who complete training after Sept. 1 but before Oct. 1. Such candidates must still submit applications by the Sept. 1 deadline.

3. The ABPN reaffirmed its policy whereby every applicant must have an unlimited license to practice medicine in a state, commonwealth or territory of the United States or a province of Canada. Every applicant is required to submit copies of current license registrations and expiration date with the application.

4. The ABPN approved the change of name for the Committee on Certification in Child Psychiatry to the Committee on Certification in Child and Adolescent Psychiatry in November 1987.

5. On June 15, 1987, the ABPN office moved from Evanston to 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015. The new telephone number is (312) 945-7900.

6. The Board sponsored a summer meeting on subspecialization in psychiatry in Vail, Colo. and met with outside consultants regarding subspecialization in forensic psychiatry, geriatric psychiatry, and alcoholism and drug addiction.

7. At its January 1988 policy meeting the Board appointed a task force, consisting of representatives from the Board and other psychiatrists and physicians, to study subspecialty certification in geriatric psychiatry and to advise the Directors about this proposal. The task force held its first meeting in April 1988 at the ABPN office. In

TABLE 2. Performance of Physicians Who Took ABPN Part II (Oral) Examinations in 1987

Examination Results	Total		Psychiatry		Neurology		Child Neurology		Graduates in U.S. and Canada				Foreign Graduates			
									New	Reexamined	Total		New	Reexamined	Total	
	N	%	N	%	N	%	N	%			N	%			N	%
Passed and certified	1,103	59	779	56	287	68	37	62	687	213	900	65	85	118	203	41
Failed	779	41	624	44	132	32	23	38	315	170	485	35	91	203	294	59
Total	1,882	100	1,403	100	419	100	60	100	1,002	383	1,385	100	176	321	497	100

addition to the ABPN, the American Board of Medical Specialties must approve any certificate in a subspecialty.

8. The Board's steering committee on recertification continues to review this issue. The committee is working closely with APA's task force on recertification.

9. At the 1987 APA annual meeting the ABPN again offered a workshop titled "ABPN and RRC Update." Members of the Residency Review Committee joined the ABPN psychiatry Directors to present information about both bodies and to respond to questions. In addition, the Executive Secretary and psychiatry Board Directors have participated in plenary sessions and other workshops of APA and the American Association of Directors of Psychiatric Residency Training in an attempt to minimize misunderstandings and to publicize current issues of the Board. A workshop will also be held at the 1988 APA annual meeting.

10. At the November 1987 meeting of the American Association of Medical Colleges and the April 1988 meeting of the American Academy of Neurology, ABPN neurology Directors and the Executive Secretary met with the Association of University Professors of Neurology to discuss current issues of the Board and to respond to questions. This meeting proved valuable in outlining the Board's current policies and training requirements.

11. Dr. Marc Hollender continues to update the history of the Board with the assistance of Dr. S. Mouchly Small.

12. The Board will hold a meeting in July 1988 to discuss general business items and to study examination validity. During this time the steering committee on recertification will also meet to continue reviewing the issue of recertification. The Board will also review the report of the task force to study subspecialty certification in geriatric psychiatry.

13. The Board is in the process of revising the definitions of specialists, which will appear in a future edition of the American Board of Medical Specialties informational brochure *Definition of a Specialist*.

14. Computer programming that enables the Board to provide information on Board examination results to training program directors has been completed. Batch data indicating pass/fail totals by year for individual programs are available. In addition, data by name are available beginning with candidates who submitted new applications for the Board's 1987 part I examination. Data are available to a training director for his or her program only and only if requested in writing. Requests should be sent to the ABPN office. This information, particularly the data provided by name, is confidential and should not be distributed by training directors to other individuals.

Child and Adolescent Psychiatry

The members of the 1987 Committee on Certification in Chil and Adolescent Psychiatry were Dr. John E. Schowalter, Chair; Dr Peter E. Tanguay, Vice-Chair; Dr. Donald S. Gair, Secretary-Treas urer; Dr. Joseph Fischhoff; Dr. Iris Litt (representative from th American Board of Pediatrics); Dr. William H. Sack; and Dr. Joel P Zrull.

The members of the 1988 Committee on Certification in Chil and Adolescent Psychiatry are Dr. Joseph Fischhoff, Chair; Dr. Joe P. Zrull, Vice-Chair; Dr. Donald S. Gair, Secretary-Treasurer; Dr Lois T. Flaherty; Dr. Iris F. Litt (representative from the Americai Board of Pediatrics); Dr. William H. Sack; Dr. Theodore Shapiro and Dr. Joel P. Zrull.

Each member of the Committee on Certification in Child an Adolescent Psychiatry is elected to serve one 6-year term and is no eligible for reelection.

At its Sept. 18–20, 1987, examination in Minneapolis, the com mittee examined 194 candidates; 129 (66%) passed, 21 (11%) con ditioned the examination, and 44 (23%) failed. The 1988 examina tion will be held Sept. 23–25, in Washington, D.C.. The 198 examination will be held Sept. 15–17, in Atlanta. Applications ar due the May 1 preceding the examination and are available from th Board office.

Other items of interest and decisions made by the Committee o Certification in Child and Adolescent Psychiatry are as follows:

1. The committee requested approval from the ABPN for change in the committee name to the Committee on Certification i Child and Adolescent Psychiatry. Approval was given, and thi change became effective in November 1987.

2. The committee elected Dr. Lois T. Flaherty (Institute of Psy chiatry and Human Behavior, Baltimore) and Dr. Theodore Shapir (Cornell University Medical College, New York) to succeed Dr. Joh E. Schowalter and Dr. Peter E. Tanguay as members of the commit tee effective Jan. 1, 1988. The terms of Drs. Schowalter and Tangua ended Dec. 31, 1987.

3. The following 1988 officers were elected: Dr. Joseph Fischhoff Chair; Dr. Joel P. Zrull, Vice-Chair; Dr. Donald S. Gair, Secretary Treasurer.

4. The 1987 examination was the first one to be held on a week end. The weekend format was well received by candidates, examin ers, and facilities hosting the examinations. All future examination arranged to date have been scheduled on weekends.

5. The committee nominated Dr. Kenneth Robson (Institute o Living, Hartford, Conn.) as a member to succeed Dr. Donald S Gair, whose term expires Dec. 31, 1988. The ABPN has approve the nomination. His term will begin Jan. 1, 1989.

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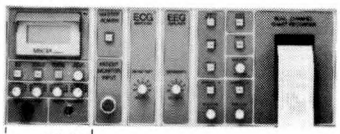
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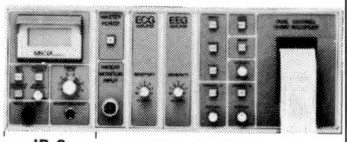


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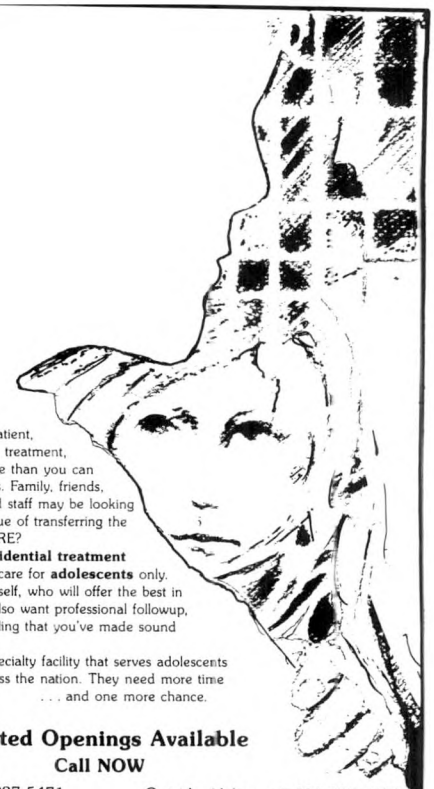
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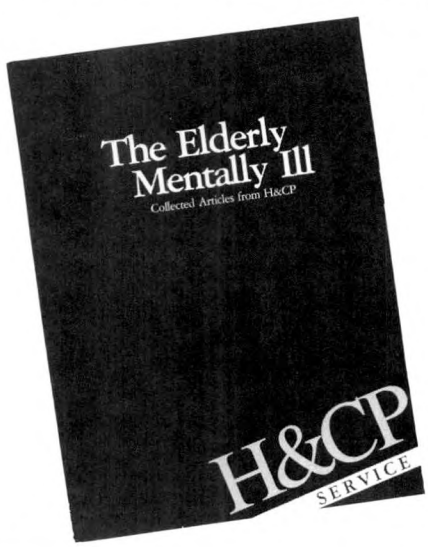
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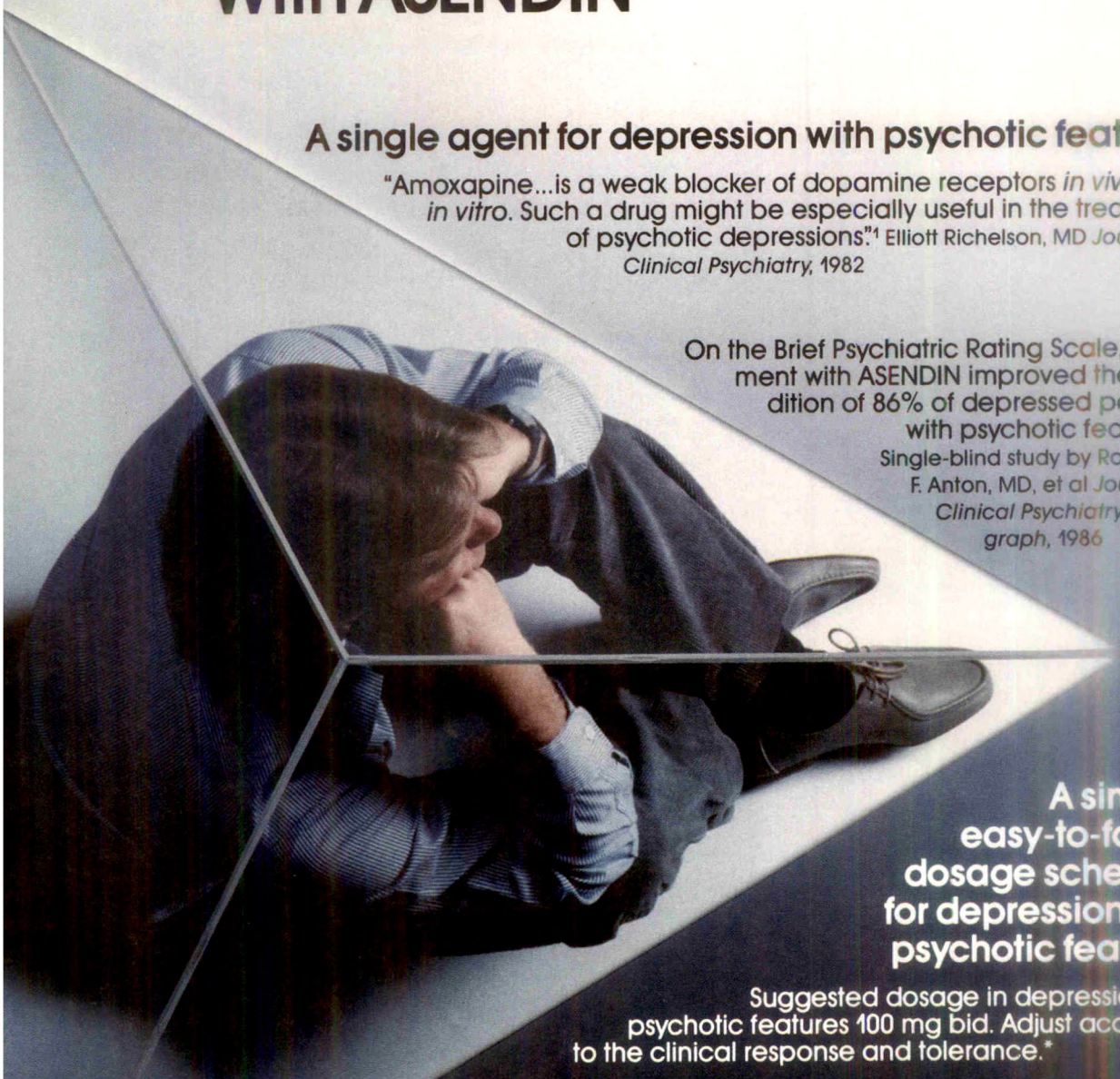
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INDICATIONS: ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.

CONTRAINDICATIONS: Prior hypersensitivity to dibenzoxazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.

WARNINGS: Tardive dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on **Information for the patient** and **ADVERSE REACTIONS.**)

Neuroleptic malignant syndrome (NMS): A potentially fatal symptom complex. NMS has been reported in association with antipsychotic drugs. Clinical manifestations are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Diagnosis is complicated. Rule out serious medical illness (eg, pneumonia, systemic infection) and inadequately treated extrapyramidal symptoms (EPS). Other considerations in differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology. Management of NMS includes immediate discontinuation of antipsychotic and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of concomitant serious medical problems for which specific treatments are available. Reintroduction of antipsychotic drug treatment after recovery from NMS should be carefully considered and closely monitored since recurrences of NMS have been reported.

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase. Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN *amoxapine* should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in <1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported. **Information for the patient:** It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired. **Drug interactions:** See **CONTRAINDICATIONS** regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered. **Therapeutic interactions:** Concurrent administration with electroshock may increase hazards associated with such therapy. **Carcinogenesis, Impairment of fertility:** In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length. **Pregnancy: Pregnancy Category C:** Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers:** ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women. **Pediatric use:** Safety and effectiveness in children below the age of 16 have not been established.

ADVERSE REACTIONS: Reported in Controlled Studies: **Incidence greater than 1%**—Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).

Less frequently reported reactions were: **CNS and neuromuscular**—anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns. **Allergic**—edema, skin rash. **Endocrine**—elevation of prolactin levels. **Gastrointestinal**—nausea. **Other**—dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration. **Incidence less than 1%—Anticholinergic**—disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness. **Cardiovascular**—hypotension, hypertension, syncope, tachycardia. **Allergic**—drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis. **CNS and neuromuscular**—tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. (See WARNINGS.) **Hematologic**—leukopenia, agranulocytosis. **Gastrointestinal**—epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea. **Endocrine**—increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion. **Other**—lacrimation, weight gain or loss, altered liver function, painful ejaculation. **Drug relationship unknown:** Reported rarely, but under circumstances where drug relationship was unknown: **Anticholinergic**—paralytic ileus. **Cardiovascular**—atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block. **CNS and neuromuscular**—hallucinations. **Hematologic**—thrombocytopenia, eosinophilia, purpura, petechiae. **Gastrointestinal**—parotid swelling. **Endocrine**—change in blood glucose levels. **Other**—pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.

Additional adverse reactions reported with other antidepressant drugs: Anticholinergic—sublingual adenitis, dilation of the urinary tract. **CNS and neuromuscular**—delusions. **Gastrointestinal**—stomatitis, black tongue. **Endocrine**—gynecomastia.

OVERDOSAGE: Signs and symptoms

Toxic manifestations of ASENDIN *amoxapine* overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.

Treatment

Treatment of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (*N Engl J Med* 1982; 306:1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for nondrug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is *not* a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients

Rev. 11/87

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1. Richelson E: Pharmacology of antidepressants in use in the United States. *J Clin Psychiatry* 1982;43:4-11
2. Anton RF, Hitri A, Diamond BI, et al: Amoxapine treatment of psychotic depression: dose effect and dopamine blockade. *J Clin Psychiatry Monograph* 1986,4:32-36.

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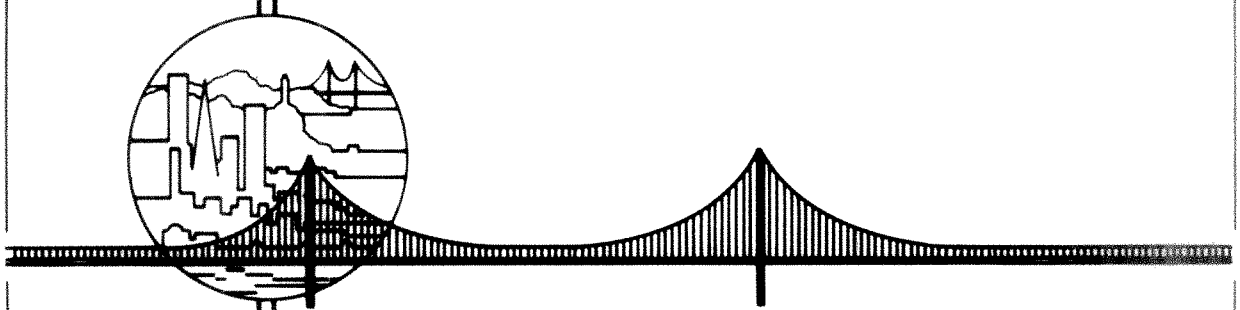
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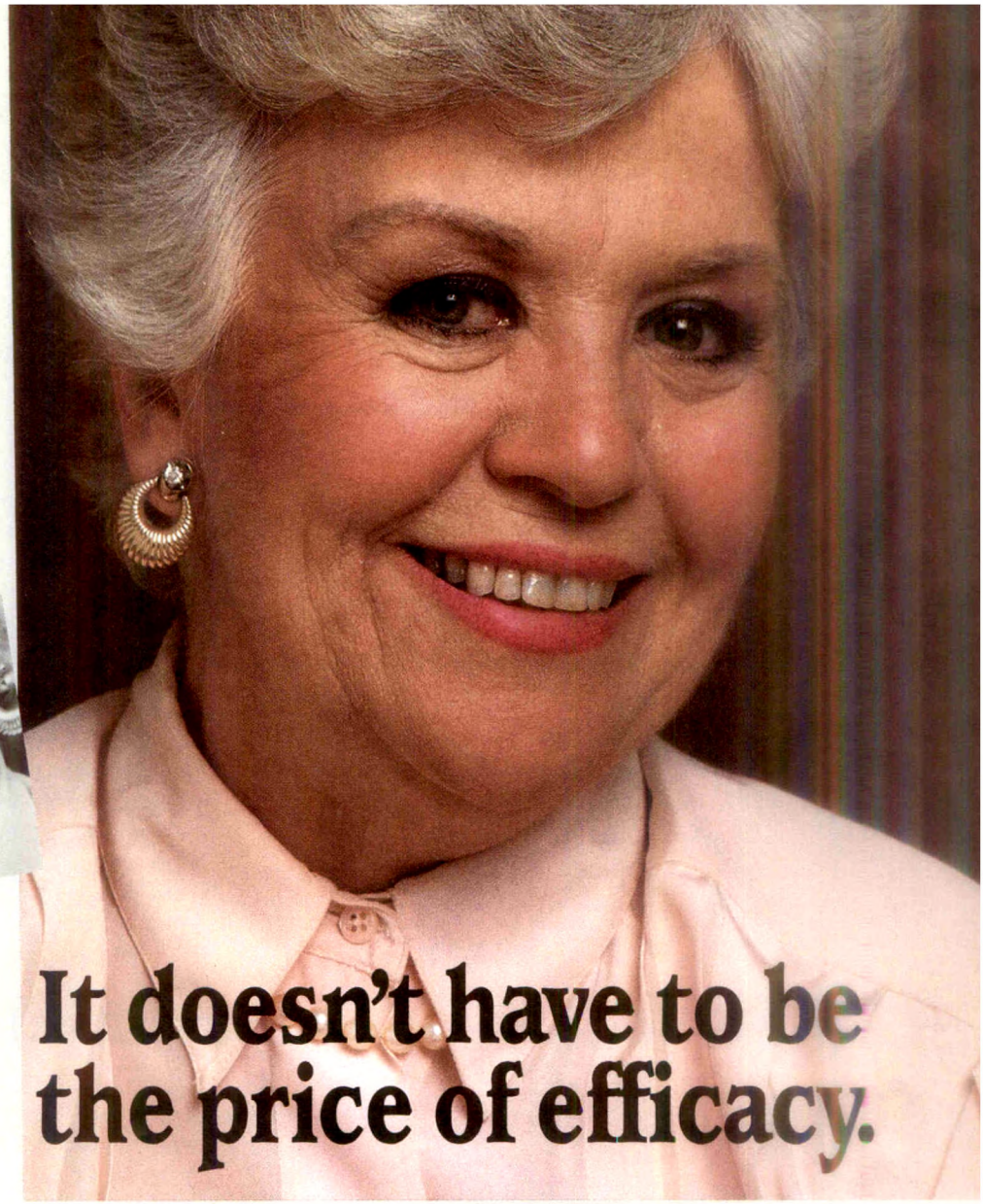
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For Brief Summary, please see following page.

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References: 1. Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26. **2.** Newton RE, *et al*: A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. **3.** Mattila MJ, *et al*: Acute effects of buspirone and alcohol on psychomotor skills. *J Clin Psychiatry* 1982;43(12,Sec 2):56-60.

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: *General*—*Interference with cognitive and motor performance:*** Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

***Information for Patients*—**Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only if clearly needed.

***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.

***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of age.

***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

***Incidence in Controlled Clinical Trials*—**Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

***Other Events Observed During the Entire Pre-marketing Evaluation*—**The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

***Physical and Psychological Dependence*—**Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

***Recommended Overdose Treatment*—**General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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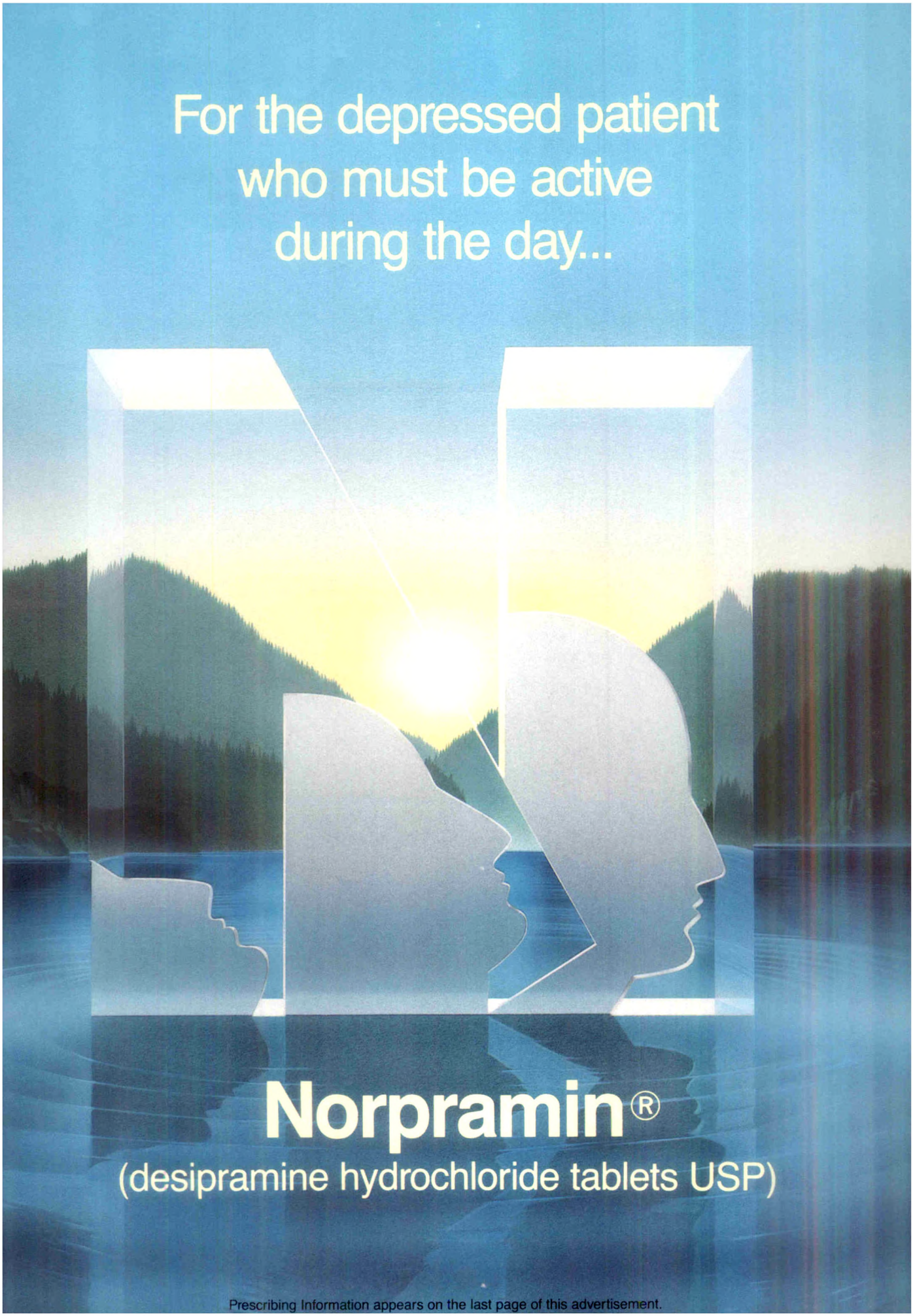
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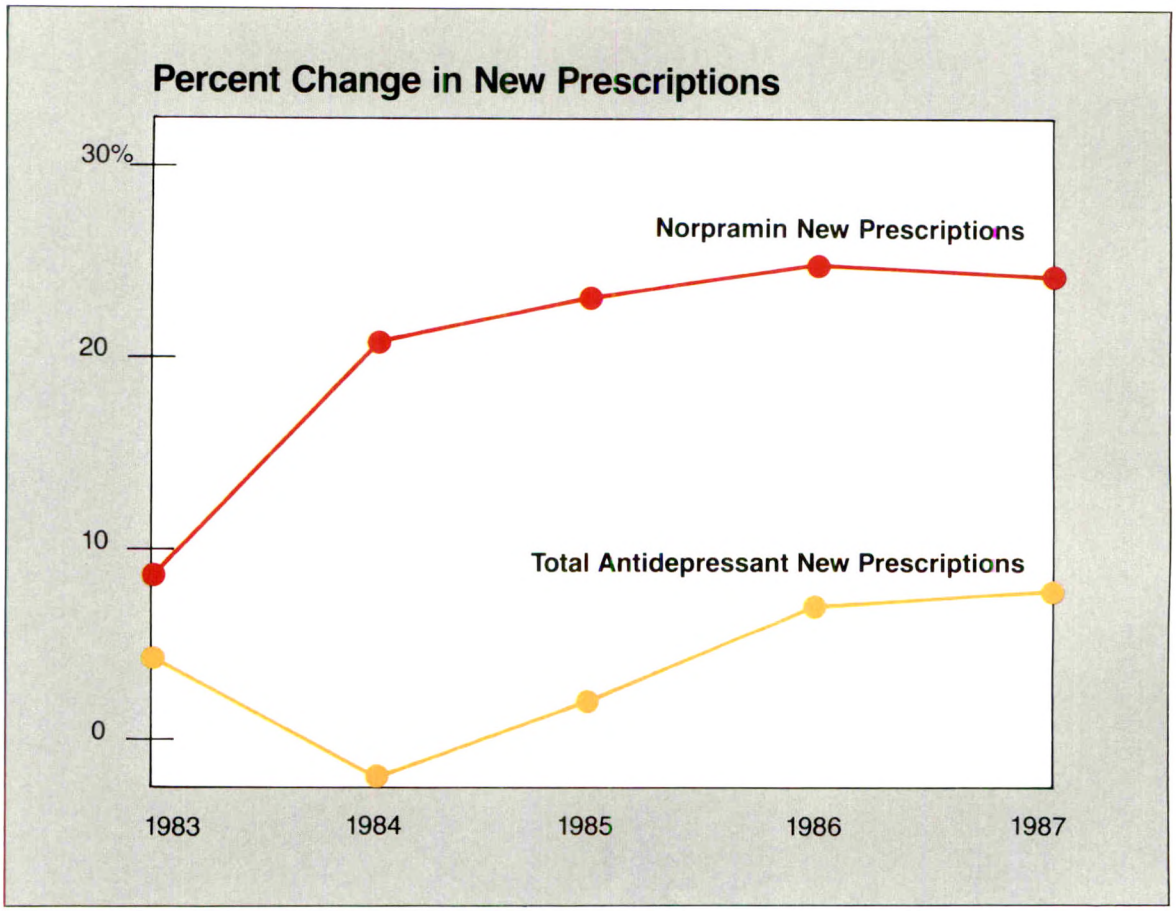


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*Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

References:

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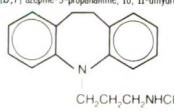
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Norpramin (desipramine hydrochloride USP) is an antidepressant drug of the tricyclic type, and is chemically: 5*H*-Dibenz [*b*, *f*] azepine-5-propanamine, 10, 11-dihydro-*N*-methyl-, monohydrochloride



INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: ACAcia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Mechanism of Action

Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindoleacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

Metabolism

Tricyclic antidepressants, such as desipramine hydrochloride, are rapidly absorbed from the gastrointestinal tract. Tricyclic antidepressants or their metabolites are to some extent excreted through the gastric mucosa and reabsorbed from the gastrointestinal tract. Desipramine is metabolized in the liver and approximately 70% is excreted in the urine.

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. Up to a thirty-sixfold difference in plasma level may be noted among individuals taking the same oral dose of desipramine. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Research on the relationship of plasma level to therapeutic response with the tricyclic antidepressants has produced conflicting results. While some studies report no correlation, many studies cite therapeutic levels for most tricyclics in the range of 50 to 300 nanograms per milliliter. The therapeutic range is different for each tricyclic antidepressant. For desipramine, an optimal range of therapeutic plasma levels has not been established.

INDICATIONS

Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**

   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**

   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established.
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants (see CLINICAL PHARMACOLOGY, *Metabolism*). Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation, insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy, extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling, elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling, drowsiness, dizziness; weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Not recommended for use in children.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose

The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response. Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of the QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Adolescent and Geriatric Dose

The usual adolescent and geriatric dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose, no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. *In vitro* experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

HOW SUPPLIED

10 mg blue coated tablets imprinted 68-7
- NDC 0068-0007-01: bottles of 100

25 mg yellow coated tablets imprinted MERRELL 11 or NORPRAMIN 25
- NDC 0068-0011-01: bottles of 100
- NDC 0068-0011-61: unit dose dispenser of 100
- NDC 0068-0011-10: bottles of 1000

50 mg green coated tablets imprinted MERRELL 15 or NORPRAMIN 50
- NDC 0068-0015-01: bottles of 100
- NDC 0068-0015-61: unit dose dispenser of 100
- NDC 0068-0015-10: bottles of 1000

75 mg orange coated tablets imprinted MERRELL 19 or NORPRAMIN 75
- NDC 0068-0019-01: bottles of 100

100 mg peach coated tablets imprinted MERRELL 20 or NORPRAMIN 100
- NDC 0068-0020-01: bottles of 100

150 mg white coated tablets imprinted MERRELL 21 or NORPRAMIN 150
- NDC 0068-0021-50: bottles of 50

Norpramin tablets should be stored at room temperature, preferably below 86°F (30°C). Protect from excessive heat.

Product Information as of April, 1987 Y?90D

MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

8-0110(NR047) MDA037

November, 1987

Printed in U.S.A.

Calendar

(Continued from page A21)

rector, Office of International Affairs, APA, 1400 K St., N.W., Washington, DC 20005; 202-682-6286.

October 13–19, Eighth World Congress of Psychiatry, World Psychiatric Association, Athens, Greece. Contact Dr. Constantin R. Soldatos, Department of Psychiatry, Eginition Hospital, 74 Vassilissis Sophias Avenue, Athens 11528 Greece, 30 1 72 23 670.

October 14–16, biennial meeting, 6th International Conference on Psychonephrology, Chicago. Contact Norman B. Levy, M.D., Director, Liaison Psychiatry Division, Westchester County Medical Center, Valhalla, NY 10595; 914-285-8424.

October 15–20, annual meeting, American Academy of Pediatrics, San Francisco. Contact James E. Strain, M.D., Executive Director, P.O. Box 927, Elk Grove Village, IL 60009-0927; 312-288-5005.

October 16–18, part II examinations, American Board of Psychiatry and Neurology, Chicago. Contact Stephen C. Scheiber, M.D., Executive Secretary, ABPN, 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015; 312-945-7900.

October 16–20, annual meeting, American Health Care Association, Anaheim, Calif. Contact Paul R. Willging, Ph.D., Executive Vice President, 1200 15th St., N.W., 8th Fl., Washington, DC 20005-2899; 202-833-2050.

October 18–20, II World Congress of Chronical Roncopathy, Unidad Docente de Valle Hebrón, Barcelona. Contact BRP–Barcelona Relaciones Públicas, Edificio Layetana C/ Pau Calris, 138, 7º 4ª 08009–Barcelona; 93-215-72-14.

October 18–21, annual meeting, American Neurological Association, San Francisco. Contact Jan W. Kolehmainen, Executive Director, P.O. Box 14730, Minneapolis, MN 55414; 612-378-3290.

October 19–20, annual meeting, Institute of Medicine/National Academy of Sciences, Washington, D.C. Contact Samuel O. Thier, M.D., President, 2101 Constitution Ave., Washington, DC 20418; 202-334-2169.

October 19–22, annual meeting, Canadian Mental Health Association, Charlottetown, Canada. Contact George Rohn, General Director, 2160 Yonge St., 3rd Fl., Toronto, Ontario, Canada M4S 2Z3; 416-484-7750.

October 20–22, biannual meeting, International Psychiatric Association for the Advancement of Electrotherapy, Portland, Ore. Contact Barry M. Maletzky, M.D., President, IPAAE, 8332 S.E. 13th Ave., Portland, OR 97202; 503-238-5580.

October 20–23, annual meeting, American Academy of Psychiatry and the Law, San Francisco. Contact Jonas R. Rappeport, M.D., Medical Director, 1211 Cathedral St., Baltimore, MD 21201; 301-539-0379.

October 22–27, Hospital & Community Psychiatry Institute, New Orleans. Contact Susan Kuper, American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005, 202-682-6174.

October 23–26, annual meeting, Society for Traumatic Stress Studies, Dallas. Contact The Society for Traumatic Stress Studies, P.O. Box 1564, Lancaster, PA 17603-1564.

October 23–28, annual meeting, American College of Surgeons, Chicago. Contact Paul A. Ebert, M.D., Director, 55 East Erie St., Chicago, IL 60610; 312-664-4050.

October 26–30, annual meeting, Academy of Psychosomatic Medicine, New Orleans. Contact Evelyne Hallberg, Executive Director, 5824 N. Magnolia, Chicago, IL 60660; 301-784-2025.

October 26–30, annual meeting, American Academy of Child and Adolescent Psychiatry, Seattle. Contact Virginia Q. Anthony, Executive Director, 3615 Wisconsin Ave., N.W., Washington, DC 20016; 202-966-7300.

October 27–30, annual conference, American Association for Marriage and Family Therapy, New Orleans. Contact Diane Sollee, N.S.W., Conference Director, AAMFT, 1717 K St., N.W., #407, Washington, DC 20006; 202-429-1825.

October 28, Shenandoah Bio-Behavioral Conference – 5, Roanoke, Va. Contact Frank F. Tallian, M.D., Psychiatric Education Center (7–1), VA Medical Center, Salem, VA 24153; 703-982-2463, ext. 2515.

October 28–30, annual meeting, Epilepsy Foundation of America, Washington, D.C. Contact William M. McLin, Executive Vice-President, 4351 Garden City Dr., Suite 406, Landover, MD 20785; 301-459-3700.

October 28–November 7, First International Congress in Emergency Psychiatry, Saint-Denis, Reunion Island. Contact Dr. J. Hoareau, 242 bis, Boulevard Saint-Germain, 75007 Paris, France.

October 29–November 5, 3rd Peruvian/Ecuadorian Congress of Psychiatry, Peruvian Psychiatric Association, Lima, Peru. Contact Dr. Roberto Llanos Z., Clinica Ricardo Palma, Av. Javier Prado Este 1038 Of. 201, Lima 27, Peru;

(Continued on page A42)

Calendar

(Continued from page A41)

014-409180 or Dr. Luis Vasquez, MILA, 38760 Northwoods Dr., Wadsworth, IL 60083; 312-249-1900.

October 30–November 2, Southern Regional Conference on Mental Health Statistics, New Orleans. Contact Ms. Olivia Williams, Chairperson, Southern Regional Conference on Mental Health Statistics, Santee-Wateree Mental Health Center, P.O. Box 1946, Sumter, SC 29151; 803-775-9364.

October 30–November 3, annual meeting, Association of Mental Health Clergy, Minneapolis. Contact George E. Doebler, M. Div., Executive Director, 12320 River Oaks Point, Knoxville, TN 37922; 615-544-9717.

October 30–November 4, annual meeting, Association of Military Surgeons of the United States, San Antonio, Tex. Contact Lt. General Max B. Bralliar, Executive Director, P.O. Box 104, Kensington, MD 20895; 301-933-2801.

NOVEMBER

November 2–6, annual meeting, American Art Therapy Association, Inc., Boston. Contact Edward J. Stygar, Jr., Executive Director, 505 E. Hawley St., Mundelein, IL 60060; 312-949-6064.

November 2–9, First Regional Andean Meeting on Psychiatry, Peruvian Psychiatric Association, Cusco, Peru. Contact Dr. R. Llanos Z., Asociacion Psiquiatrica Peruana, Avenida Javier Prado Este 1038-201, Lima 27, Peru.

November 4–6, Ninth Annual Conference, The National Association for Drama Therapy, Los Angeles. Contact Dr. Pamela Barragar Dunne, Conference Head, NADT, California State University, Los Angeles, Dept. of Theatre Arts and Dance, 5151 State University Dr., Los Angeles, CA 90032; 213-224-3285.

November 6–10, 12th Congress, World Association for Social Psychiatry, London. Contact Conference Associates WASP, 27A Medway St., Westminster, London SW1P 2BD, United Kingdom; 01-222-9493; Telex 934346 CONFAS G; Facsimile 01-222 4246

November 9–13, annual meeting, American Dance Therapy Association, Baltimore. Contact Stephanie Katz, President, 2000 Century Plaza, Suite 108, Columbia, MD 21044; 301-997-4040.

November 10–13, Assembly of District Branches, American Psychiatric Association, Washington, D.C.

November 11–13, First International Congress on Somatotherapy, Paris. Contact Dr. Richard Meyer, President, AJP/L'Innovation Psychiatrique, 17, rue de Lausanne, 67000 Strasbourg, France; 88-35-17-27.

November 12–17, annual meeting, Association of American Medical Colleges, Chicago. Contact Robert G. Petersdorf, M.D., President, One Dupont Circle, N.W., Suite 200, Washington, DC 20036; 202-828-0400.

November 13–17, annual meeting, American Public Health Association, Boston. Contact William H. McBeath, M.D., M.P.H., Executive Director, 1015 15th St., N.W., Washington, DC 20005; 202-789-5600.

November 13–17, Second World Congress on Drugs and Alcohol, World Association for the Prevention of Drug and Alcohol Abuse, Tel Aviv, Israel. Contact Judge Amnon Carmi, Israel Congress Committee, 10 Meryl Ln., Great Neck, NY 11024.

November 14–15, annual meeting, Council of Medical Specialty Societies, Rosemont, Ill. Contact Richard S. Wilbur, M.D., Executive Vice-President, P.O. Box 70, Lake Forest, IL 60045; 312-295-3456.

November 15–18, annual conference of the Association for Medical Education and Research in Substance Abuse, Rockville, Maryland. Contact Susan Paquin Simpson, Brown University Center for Alcohol and Addiction Studies, Box G, Providence, RI 02912, 401-863-3173.

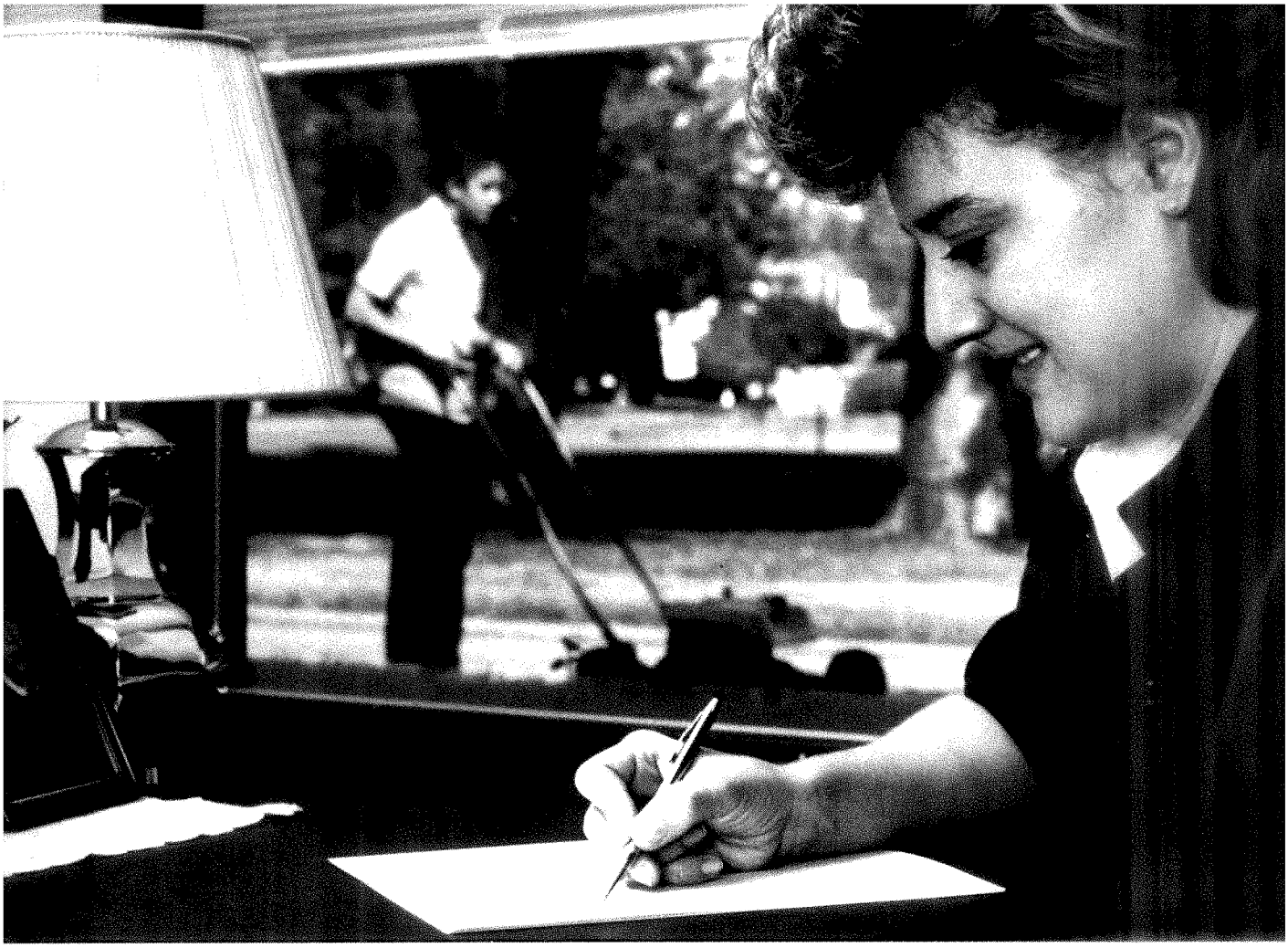
November 15–20, annual meeting, National Mental Health Association, Hartford, Conn. Contact Preston J. Garrison, Executive Director, 1021 Prince St., Alexandria, VA 22314; 703-684-7722.

November 16–20, annual meeting, American Anthropological Association, Phoenix, Ariz. Contact Edward J. Lehman, Executive Director, 1703 New Hampshire Ave., N.W., Washington, DC 20009; 202-232-8800.

November 16–21, annual meeting, Society for Neuroscience, New Orleans. Contact Nancy Beang, Executive Director, 11 Dupont Circle, N.W., Suite 130, Washington DC 20036; 202-462-6688.

November 18–22, annual meeting, National Association for Music Therapy, Inc., Atlanta. Contact Edward L. Norwood R.M.T., Executive Director, 505 11th St., S.E., Washington, DC 20003; 202-543-6864.

November 27–December 2, annual meeting, National Rehabilitation Association, Reno, Nev. Contact David L. Mills, Executive Director, 633 S. Washington St., Alexandria, VA 22314; 703-836-0850.



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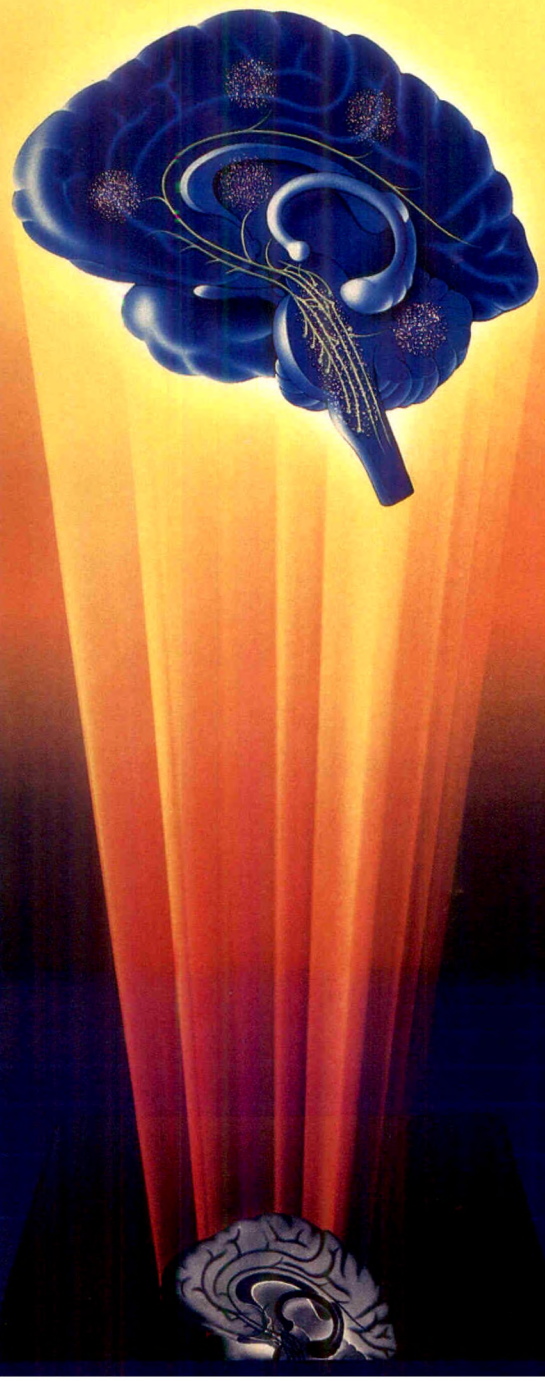
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fluoxetine hydrochloride

Brief Summary. Consult the package insert for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindications: None known.

Warnings: *Monoamine Oxidase Inhibitors*—Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General*—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of Prozac-treated patients compared to 4% of placebo and 3% of tricyclic-antidepressant-treated patients. However, only rarely have Prozac patients been discontinued for weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Life of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. (*See* Clinical Pharmacology and Dosage and Administration sections).

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 753 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

- Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.
- Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.
- Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breast feeding an infant.
- Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors—*See* Warnings.

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients.

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children—Safety and effectiveness in children have not been studied.

Use in the Elderly—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Adverse Reactions: *Commonly Observed*—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials—Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac—During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 Prozac-exposed individuals who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole—*Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System—*Infrequent:* angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block (first-degree), bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—*Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, and thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event: Prozac (N=1,730)	Placebo (N=799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	—
Light-headedness	1.6	—
Concentration, decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4

Body System/ Adverse Event*	Percentage of Patients Reporting Event: Prozac (N=1,730)
Body as a Whole	
Asthenia	4.4
Infection, viral	3.4
Pain, limb	1.6
Fever	1.4
Pain, chest	1.3
Allergy	1.2
Influenza	1.2
Respiratory	
Upper respiratory infection	7.6
Flu-like syndrome	2.8
Pharyngitis	2.7
Nasal congestion	2.6
Headache, sinus	2.3
Sinusitis	2.1
Cough	1.6
Dyspnea	1.4
Cardiovascular	
Hot flushes	1.8
Palpitations	1.3
Musculoskeletal	
Pain, back	2.0
Pain, joint	1.2
Pain, muscle	1.2
Urogenital	
Menstruation, painful	1.9
Sexual dysfunction	1.9
Frequent micturition	1.6
Urinary tract infection	1.2
Special Senses	
Vision disturbance	2.8

*Events reported by at least 1% of Prozac patients are included.
— Incidence less than 1%.

Endocrine System—*Infrequent:* hypothyroidism; *Rare:* goiter and thyroiditis.

Hemic and Lymphatic System—*Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, leukocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional—*Frequent:* weight loss; *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipidemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System—*Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System—*Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusion, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System—*Frequent:* bronchitis, rhinitis, and yawning; *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis, alveolitis, and pleural effusion.

Skin and Appendages—*Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—*Infrequent:* amblyopia, conjunctivitis, ear pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, strabismus, and taste loss.

Urogenital System—*Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare:* albumination, albuminuria, breast enlargement, dyspareunia, epididymitis, galactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Overdosage: *Human Experience*—As of December 1987, there were deaths among approximately 38 reports of acute overdose with fluoxetine either alone or in combination with other drugs and/or alcohol. One involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respectively. second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without anticonvulsant treatment (*see* Management subsection). The amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. for the two deaths noted above, all other overdose cases recovered residua.

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Additional information available to the profession on request from

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Books Received

Sharing the Children: How to Resolve Custody Problems and Get On With Your Life, by Robert E. Adler, Ph.D. Bethesda, Md., Adler & Adler, 1988, 248 pp., $17.95; $7.95 (paper).

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INDEX TO ADVERTISERS

AUGUST 1988

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BIOLOGIC SYSTEMS INC. A2

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
Serentil A15–A16

DORSEY PHARMACEUTICALS
Mellaril A28
Pamelor A19–A20

EMPLOYMENT OPPORTUNITIES A44, A48–A50

ELI LILLY & COMPANY
Prozac A45–A46

LEDERLE LABORATORIES
Asendin A31–A32

McNEIL PHARMACEUTICAL
Haldol Decanoate C3–C4

MEAD JOHNSON PHARMACEUTICAL
BuSpar A27, A35–A36

MECTA CORPORATION A30

MEETINGS & CONFERENCES A14

RESIDENTIAL HOMES/TREATMENT CENTERS .. A30, A43

ROCHE LABORATORIES
Valium A23

ROERIG DIV./PFIZER, INC.
Navane A6–A8
Sinequan A24–A26
2V Medtech A14

THE UPJOHN COMPANY
Halcion A12–A13, A29
Xanax A9–A10

WYETH/AYERST LABORATORIES
Ativan C2–A1

THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 145, Number 9 September 1988

In this issue:

Presidential Papers: 1988

Conceptual and Methodological Issues in Comparative Studies of Psychotherapy and Pharmacotherapy, II: Nature and Timing of Treatment Effects

By Irene Elkin, Paul A. Pilkonis, John P. Docherty, et al.

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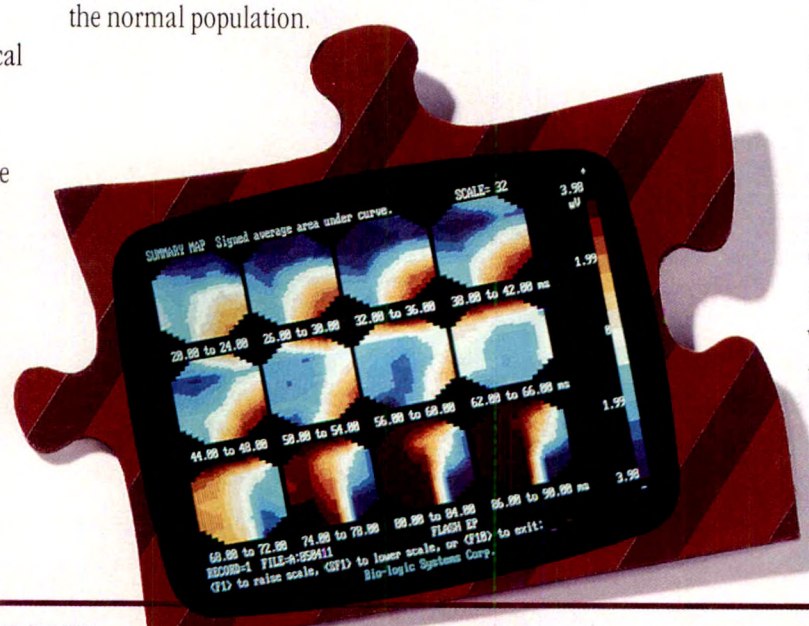
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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 145, Number 9 September 1988

PRESIDENTIAL PAPERS: 1988

1055 Presidential Address: Landfalls, Journeys, and Departures *George H. Pollock*

1061 Response to the Presidential Address: Is "Biopsychosocial" the Psychiatric Shibboleth? *Paul J. Fink*

1068 George H. Pollock, M.D., Ph.D., One Hundred Sixteenth President, 1987–1988 *Melvin Sabshin*

SPECIAL ARTICLE

1070 Conceptual and Methodological Issues in Comparative Studies of Psychotherapy and Pharmacotherapy, II: Nature and Timing of Treatment Effects *Irene Elkin, Paul A. Pilkonis, John P. Docherty, and Stuart M. Sotsky*

REGULAR ARTICLES

1077 A Multidimensional Approach to the Genetics of Schizophrenia *Robert H. Dworkin, Mark F. Lenzenweger, Steven O. Moldin, Gerald F. Skillings, and Stephen E. Levick*

1084 Comparison of MRI and CT Scans in a Group of Psychiatric Patients *Bruce M. Cohen, Ferdinando Buonanno, Paul E. Keck, Jr., Seth P. Finklestein, and Francine M. Benes*

1089 Neuroanatomical Abnormalities in Obsessive-Compulsive Disorder Detected With Quantitative X-Ray Computed Tomography *Jay S. Luxenberg, Susan E. Swedo, Martine F. Flament, Robert P. Friedland, Judith Rapoport, and Stanley I. Rapoport*

1094 Anterior Pituitary, Adrenal, and Gonadal Hormones During Cocaine Withdrawal *Jack H. Mendelson, Siew K. Teoh, Ulrike Lange, Nancy K. Mello, Roger Weiss, Alicja Skupny, and James Ellingboe*

1099 Bedside Differentiation of Depressive Pseudodementia From Dementia *Charles F. Reynolds III, Carolyn C. Hoch, David J. Kupfer, Daniel J. Buysse, Patricia R. Houck, Jacqueline A. Stack, and Donna W. Campbell*

1104 Lack of Efficacy of Carbamazepine in the Treatment of Panic Disorder *Thomas W. Uhde, Murray B. Stein, and Robert M. Post*

1110 *S*-Adenosylmethionine Treatment of Depression: A Controlled Clinical Trial *Kate M. Bell, Lawrence Plon, William E. Bunney, Jr., and Steven G. Potkin*

1115 A Randomized Clinical Trial of Inpatient Family Intervention, III: Effects at 6-Month and 18-Month Follow-Ups *James H. Spencer, Jr., Ira D. Glick, Gretchen L. Haas, John F. Clarkin, Alfred B. Lewis, Joanne Peyser, Nancy DeMane, Marcie Good-Ellis, Elizabeth Harris, and Veronica Lestelle*

1122 Four-Year Evaluation of a Psychiatric Clerkship: 1982–1986
Lynn Whisnant Reiser, William H. Sledge, and Marshall Edelson

BRIEF COMMUNICATIONS

1127 Personality Features of Obsessive-Compulsive Disorder
Russell T. Joffe, Richard P. Swinson, and Joseph J. Regan

1130 A New and Timely Delusion: The Complaint of Having AIDS
Steven L. Mahorney and Jesse O. Cavenar, Jr.

1133 Twenty-Four-Hour Profiles of Body Temperature and Plasma TSH in Bipolar Patients During Depression and During Remission and in Normal Control Subjects *Eric Souetre, Edouard Salvati, Thomas A. Wehr, David A. Sack, Bernard Krebs, and Guy Darcourt*

1138 Placebo Response in Panic Disorder *William Coryell and Russell Noyes*

1141 A Study of Filicidal Men *John F. Campion, James M. Cravens, and Fred Covan*

1145 The Relationship of Presenting Complaints to the Use of Psychiatric Services in a Low-Income Group *John M. de Figueiredo and Heidi Boerstler*

1149 *DSM-III* Personality Disorders and the Outcome of Treated Panic Disorder *James H. Reich*

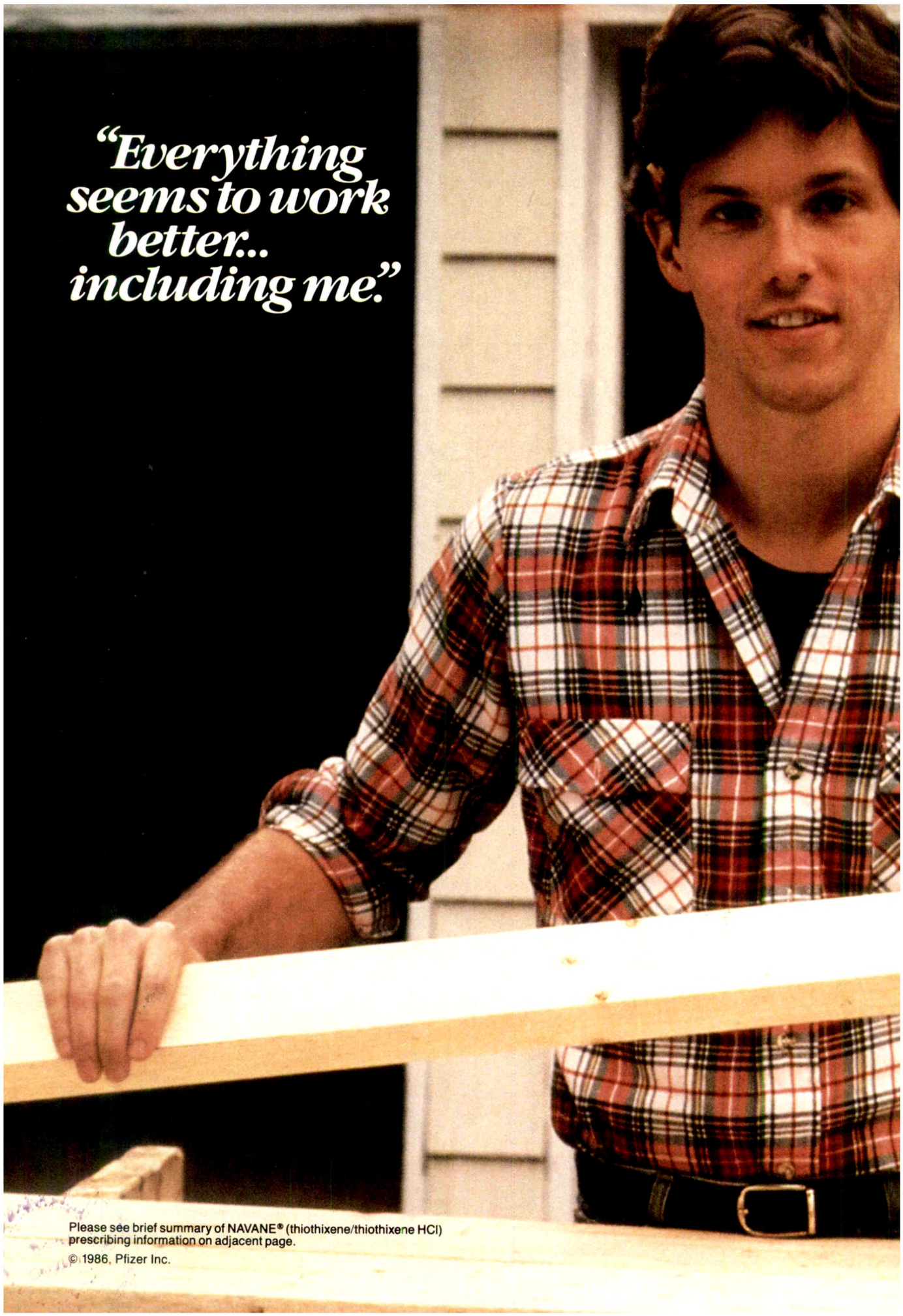
1153 DST Results in Nonpsychotic Depressed Outpatients *Arifulla Khan, Frances Johnson, David H. Avery, Seth Cohen, Beth Scherzo, and David L. Dunner*

BOOK FORUM 1157

LETTERS TO THE EDITOR 1173

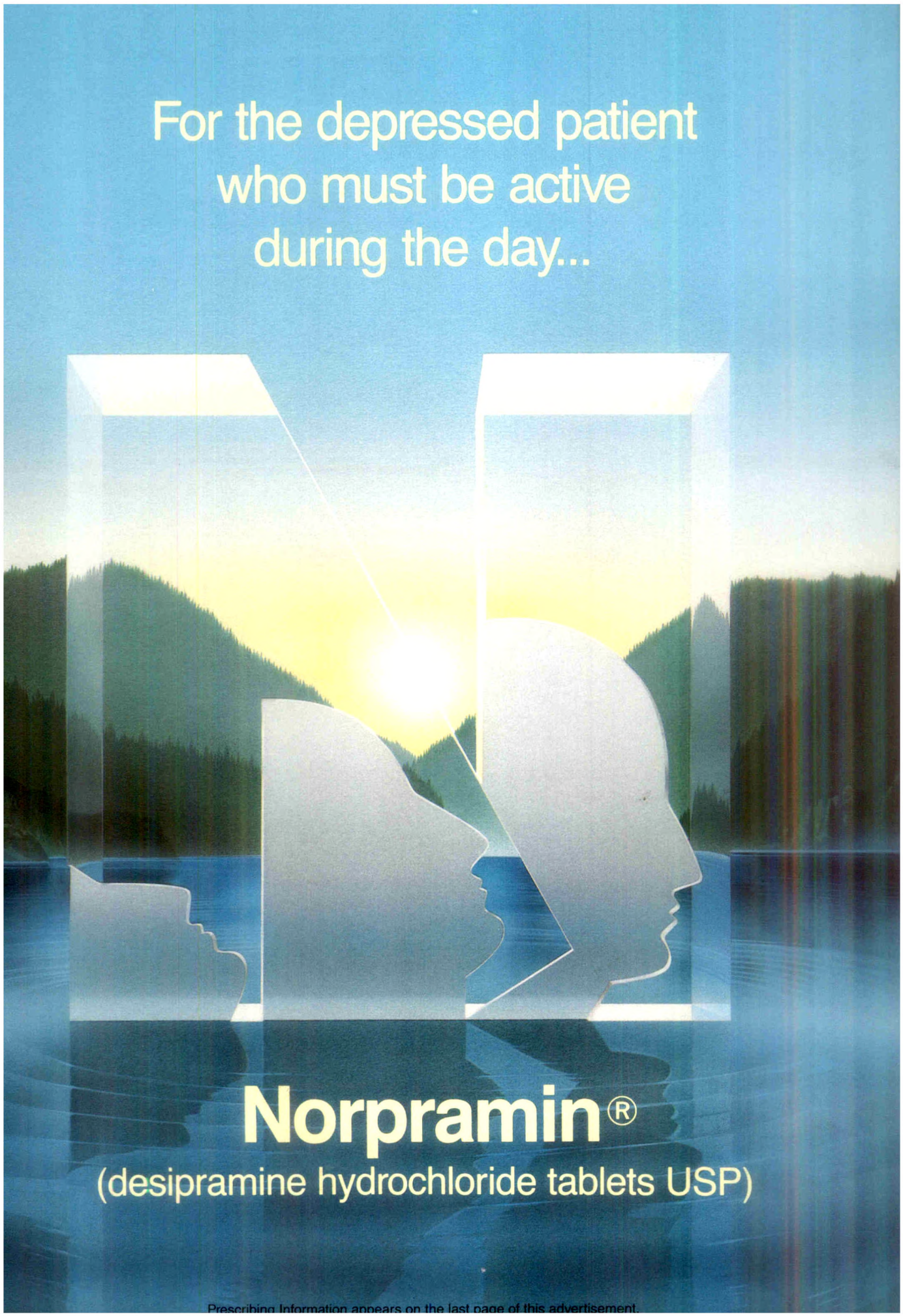
OFFICIAL ACTIONS 1187 Highlights of the 141st Annual Meeting

OTHER
1083 Deceased Members of the American Psychiatric Association
A13 Officers of the American Psychiatric Association
A20 Calendar
A35 Information for Contributors
A43 Books Received
A44 *British Journal of Psychiatry* Contents (June 1988)
A45 *British Journal of Psychiatry* Contents (July 1988)
A48 Index to Advertisers



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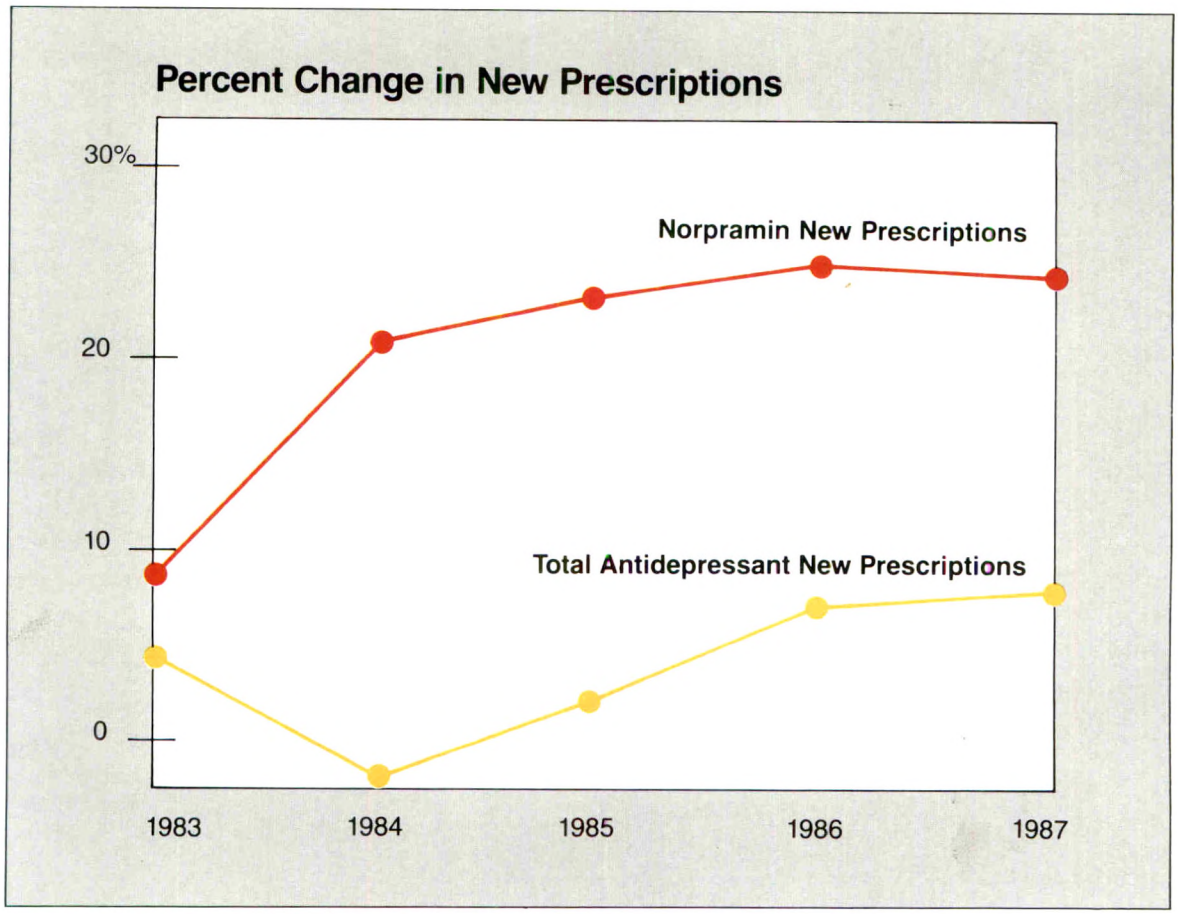


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References:

1. Nelson JC, Mazure C, Quinlan DM, and Jatlow PI: Drug responsive symptoms in melancholia. Arch Gen Psychiat 1984; 41:663-668.
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3. Snyder SH and Yamamura HI: Antidepressants and the muscarinic acetylcholine receptor. Arch Gen Psychiat 1977; 34:236-239.
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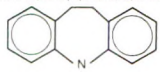
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CLINICAL PHARMACOLOGY

Mechanism of Action

Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindoleacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

Metabolism

Tricyclic antidepressants, such as desipramine hydrochloride, are rapidly absorbed from the gastrointestinal tract. Tricyclic antidepressants or their metabolites are to some extent excreted through the gastric mucosa and reabsorbed from the gastrointestinal tract. Desipramine is metabolized in the liver and approximately 70% is excreted in the urine.

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. Up to a thirty-sixfold difference in plasma level may be noted among individuals taking the same oral dose of desipramine. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Research on the relationship of plasma level to therapeutic response with the tricyclic antidepressants has produced conflicting results. While some studies report no correlation, many studies cite therapeutic levels for most tricyclics in the range of 50 to 300 nanograms per milliliter. The therapeutic range is different for each tricyclic antidepressant. For desipramine, an optimal range of therapeutic plasma levels has not been established.

INDICATIONS

Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**

   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**

   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established.
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants (see CLINICAL PHARMACOLOGY, *Metabolism*). Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities, incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus, urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Not recommended for use in children.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose

The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response. Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Adolescent and Geriatric Dose

The usual adolescent and geriatric dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response; a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physaistigmine, the effective dose should be repeated at 1-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum; even after a massive oral dose. *In vitro* experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluid. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

HOW SUPPLIED

10 mg blue coated tablets imprinted 68-7
- NDC 0068-0007-01: bottles of 100

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150 mg white coated tablets imprinted MERRELL 21 or NORPRAMIN 150
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Norpramin tablets should be stored at room temperature, preferably below 86°F (30°C). Protect from excessive heat.

Product Information as of April, 1987 Y2

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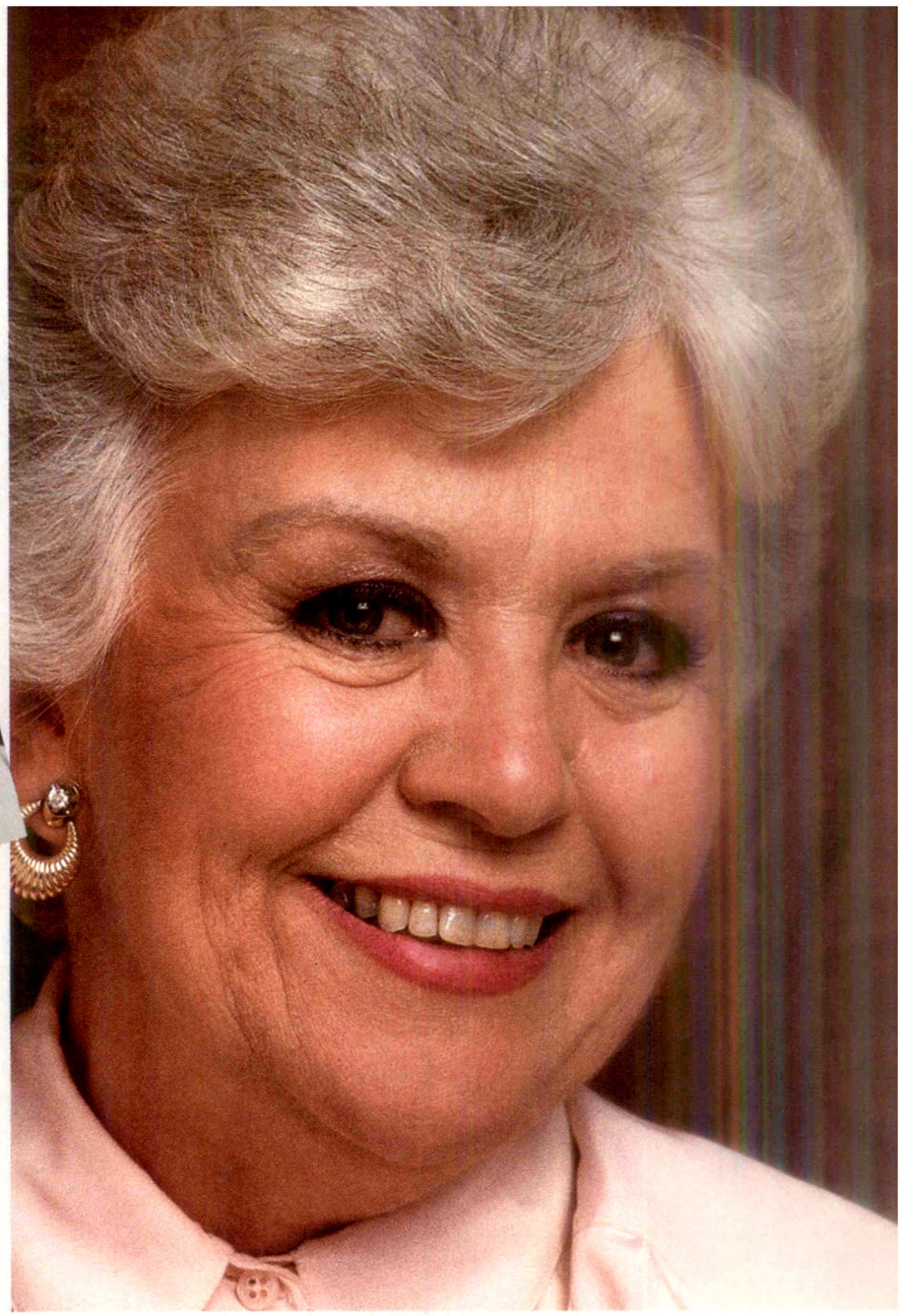
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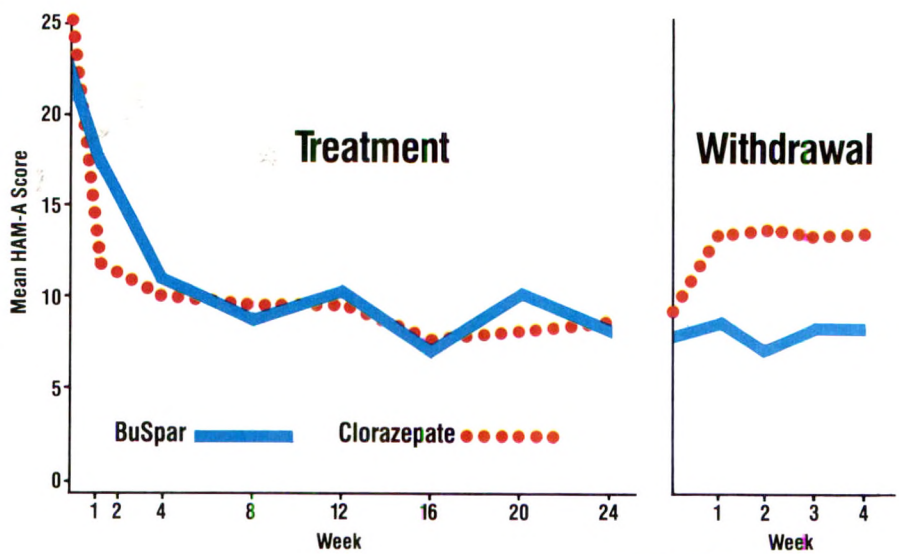
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During therapy, BuSpar-treated patients and clorazepate-treated patients experienced significant reductions in Hamilton Anxiety Scale scores. Upon discontinuation of therapy, however, clorazepate-treated patients experienced a significant increase in HAM-A Scale scores, indicating the emergence of a withdrawal syndrome —BuSpar-treated patients did not.



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The first choice for chronic anxiety

BuSpar effectively relieves the symptoms of anxiety—such as irritability, inability to concentrate, and excessive worry or fearfulness—generally without producing euphoria[2] and with no more drowsiness (10%) than induced by placebo (9%).[3]

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No withdrawal syndrome has been demonstrated in clinical trials with BuSpar, even on abrupt discontinuation of therapy.[1] As a result, you stay in control of the treatment you prescribed.

Counseling and follow-up are important. Patients should be advised that BuSpar does not produce a tranquilizer "buzz," but instead will relieve their symptoms gradually and steadily. Improvement generally is noted within 7 to 10 days. Patients should be monitored for relief of symptoms, improvement in functioning, and an increased capacity to cope.

BuSpar is not a controlled substance. Side effects associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients in controlled clinical trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

*Study conducted in normal volunteers. Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

**While formal studies of the interaction of BuSpar with alcohol indicate that it does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

The first choice for chronic anxiety

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Tablets
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(buspirone HCl)

A different kind of calm



For Brief Summary, please see following page.

BuSpar® (buspirone HCl)

References: 1. Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26. **2.** Cole JO, *et al*: Assessment of the abuse liability of buspirone in recreational sedative users. *J Clin Psychiatry* 1982;43(12,Sec 2):69-74. **3.** Newton RE, *et al*: A review of the side effect profile of buspirone. *Am J Med* 1986;80(suppl 3B):17-21. **4.** Lucki I, *et al*: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. **5.** Moskowitz H and Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. *J Clin Psychiatry* 1982;43(12,Sec 2):45-55. **6.** Mattila MJ, *et al*: Acute effects of buspirone and alcohol on psychomotor skills. *J Clin Psychiatry* 1982;43(12,Sec 2):56-60.

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (i.e., represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-marketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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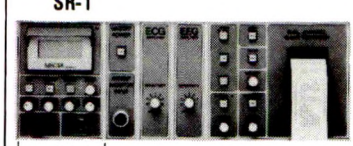
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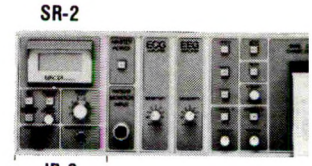


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(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml
Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.
Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.
Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.
Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damag (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patien on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should t injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadra of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, ar then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into th lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to he avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissu culture experiments indicate that approximately one third of human breast cancers are prolactin-depende *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient wi a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynec mastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels unknown for most patients. An increase in mammary neoplasms has been found in rodents after chron administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to dat however, have shown an association between chronic administration of these drugs and mammary tumo igenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics w develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, possible, full information about this risk. The decision to inform patients and/or their guardians must ol viously take into account the clinical circumstances and the competency of the patient to understand th information provided.
Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navan (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenoth azines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne i mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypoter sion occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of bloo pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navan (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therap The incidence of these changes is lower than that observed with some phenothiazines. The clinical signif cance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazine but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been note with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navar infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally relate drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal flu abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reporte Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acu symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms ma be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in som patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accom panied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing ba sis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrom If this or any other presentation of the syndrome is observed, the clinician should consider possible discor tinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, hav been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable t Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been as sociated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have bee reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced wit Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certai phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a sma percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or th discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gy necomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, i creased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines hav been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite an weight, weakness or fatigue, polydipsia and peripheral edema.

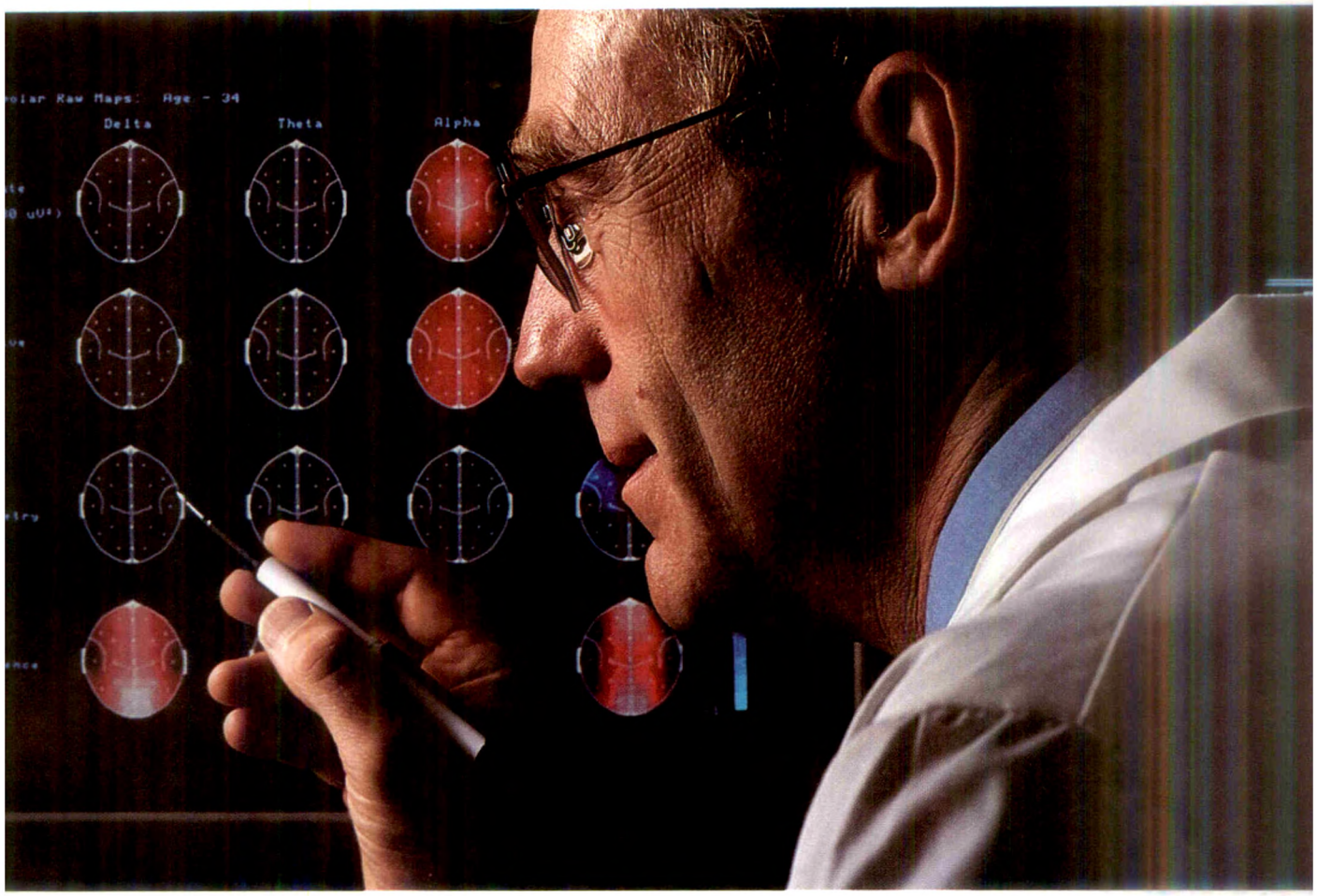
Although not reported with Navane, evidence indicates there is a relationship between phenothiazin therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNING section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenoth azine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failur of the cough reflex. In others, the cause could not be determined nor could it be established that death wa due to phenothiazine administration.
Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of th condition. See full prescribing information.
Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribin information.

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NOVEMBER

November 2–6, annual meeting, American Art Therapy Association, Inc., Boston. Contact Edward J. Stygar, Jr., Executive Director, 505 E. Hawley St., Mundelein, IL 60060; 312-949-6064.

November 2–9, First Regional Andean Meeting on Psychiatry, Peruvian Psychiatric Association, Cusco, Peru. Contact Dr. R. Llanos Z., Asociacion Psiquiatrica Peruana, Avenida Javier Prado Este 1038-201, Lima 27, Peru.

November 4–6, Ninth Annual Conference, The National Association for Drama Therapy, Los Angeles. Contact Dr. Pamela Barragar Dunne, Conference Head, NADT, California State University, Los Angeles, Dept. of Theatre Arts and Dance, 5151 State University Dr., Los Angeles, CA 90032; 213-224-3285.

November 6–10, 12th Congress, World Association for Social Psychiatry, London. Contact Conference Associates WASP, 27A Medway St., Westminster, London SW1P 2BD, United Kingdom; 01-222-9493; Telex 934346 CONFAS G; Facsimile 01-222 4246

November 9–13, annual meeting, American Dance Therapy Association, Baltimore. Contact Stephanie Katz, President, 2000 Century Plaza, Suite 108, Columbia, MD 21044; 301-997-4040.

November 10–13, Assembly of District Branches, American Psychiatric Association, Washington, D.C.

November 11–13, First International Congress on Somatotherapy, Paris. Contact Dr. Richard Meyer, President, AJP/L'Innovation Psychiatrique, 17, rue de Lausanne, 67000 Strasbourg, France; 88-35-17-27.

November 11–13, World Forensic Psychiatry and Psychology Association (First International Scientific Congress), Paris. Contact Dr. Serge Bornstein, President, World Forensic Psychiatry and Psychology Association, 18, rue de Vezelay, 750008 Paris, France.

November 12–17, annual meeting, Association of American Medical Colleges, Chicago. Contact Robert G. Petersdorf, M.D., President, One Dupont Circle, N.W., Suite 200, Washington, DC 20036; 202-828-0400.

November 13–17, annual meeting, American Public Health Association, Boston. Contact William H. McBeath, M.D., M.P.H., Executive Director, 1015 15th St., N.W., Washington, DC 20005; 202-789-5600.

November 13–17, Second World Congress on Drugs and Alcohol, World Association for the Prevention of Drug and Alcohol Abuse, Tel Aviv, Israel. Contact Judge Amnon Carmi, Israel Congress Committee, 10 Meryl Ln., Great Neck, NY 11024.

November 14–15, annual meeting, Council of Medical Specialty Societies, Rosemont, Ill. Contact Richard S. Wilbur, M.D., Executive Vice-President, P.O. Box 70, Lake Forest, IL 60045; 312-295-3456.

November 15–18, annual conference of the Association for Medical Education and Research in Substance Abuse, Rockville, Maryland. Contact Susan Paquin Simpson, Brown University Center for Alcohol and Addiction Studies, Box G, Providence, RI 02912, 401-863-3173.

November 15–20, annual meeting, National Mental Health Association, Hartford, Conn. Contact Preston J. Garrison, Executive Director, 1021 Prince St., Alexandria, VA 22314; 703-684-7722.

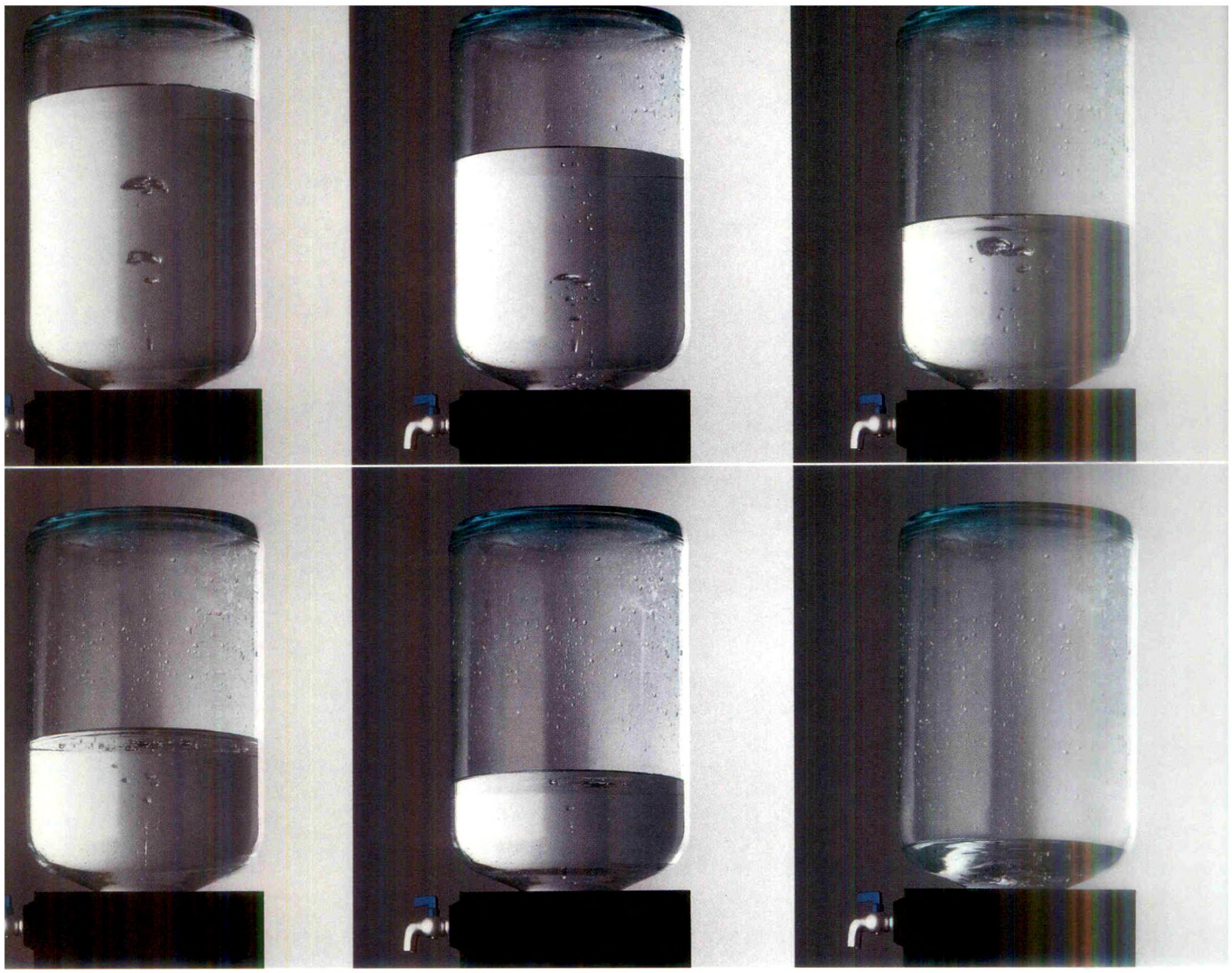
November 16–20, annual meeting, American Anthropological Association, Phoenix, Ariz. Contact Edward J. Lehman, Executive Director, 1703 New Hampshire Ave., N.W., Washington, DC 20009; 202-232-8800.

November 16–21, annual meeting, Society for Neuroscience, New Orleans. Contact Nancy Beang, Executive Director, 11 Dupont Circle, N.W., Suite 130, Washington DC 20036; 202-462-6688.

November 18–22, annual meeting, National Association for Music Therapy, Inc., Atlanta. Contact Edward L. Norwood R.M.T., Executive Director, 505 11th St., S.E., Washington, DC 20003; 202-543-6864.

November 27–December 2, annual meeting, National Rehabilitation Association, Reno, Nev. Contact David L. Mills, Executive Director, 633 S. Washington St., Alexandria, VA 22314; 703-836-0850.

November 30–December 4, International Conference on Stress, The American Institute of Stress, Montreux, Switzerland. Contact Ms. Anne Barone, Clinique Bon Port, Biotonus, CH-1820, Montreux rue du Bon Port 21, Switzerland, 021-963-5101.



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References: 1. Thompson TL II, Thompson WL: Treating depression: Tricyclics, tetracyclics, and other options. *Modern Medicine* 1983;51(August):87-109. **2.** Georgotas A: Affective disorders: Pharmacotherapy, in Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry IV* Baltimore, Williams & Wilkins, 1985, vol 1, pp 821-833. **3.** Bye C, Clubley M, Peck AW: Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol* 1978;6:155-161. **4.** Kupfer DJ, Spiker DG, Rossi A, et al: Nortriptyline and EEG sleep in depressed patients. *Biol Psychiatry* 1982;17:535-546. **5.** Blackwell B, Peterson GR, Kuzma RJ, et al: The effect of five tricyclic antidepressants on salivary flow and mood in healthy volunteers. *Communications in Psychopharmacol* 1980;4:255-261. **6.** Roose SP, Glassman AH, Siris SG, et al: Comparison of imipramine- and nortriptyline-induced orthostatic hypotension: A meaningful difference. *J Clin Psychopharmacol* 1981;1:316-319. **7.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 413-423. **8.** Thayssen P, Bjerre M, Kragh-Sorensen P, et al: Cardiovascular effects of imipramine and nortriptyline in elderly patients. *Psychopharmacology* 1981;74:360-364. **9.** Ziegler VE, Clayton PJ, Biggs JT: A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry* 1977;34:607-612.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmi heart block, stroke. *Psychiatric*—Confusional states (especially the elderly) with hallucinations, disorientation, delusions; anxi restlessness, agitation; insomnia, panic, nightmares; hypomar exacerbation of psychosis. *Neurologic*—Numbness, tingling, p esthesias of extremities; incoordination, ataxia, tremors; periphe neuropathy; extrapyramidal symptoms; seizures, alteration in E patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, asso ated sublingual adenitis; blurred vision, disturbance of accomm dation, mydriasis; constipation, paralytic ileus; urinary retenti delayed micturition, dilation of the urinary tract. *Allergic*—S rash, petechiae, urticaria, itching, photosensitization (avoid exc sive exposure to sunlight); edema (general or of face and tongu drug fever, cross-sensitivity with other tricyclic drugs. *Hematolo* —Bone-marrow depression, including agranulocytosis; eosir philia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea a vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, s matitis, abdominal cramps, black-tongue. *Endocrine* Gynecomastia in the male, breast enlargement and galactorrhea the female; increased or decreased libido, impotence; testicu swelling; elevation or depression of blood sugar levels; syndrome inappropriate ADH (antidiuretic hormone) secretion. *Other* Jaundice (simulating obstructive), altered liver function; weight g or loss; perspiration; flushing; urinary frequency, nocturia; drow ness, dizziness, weakness, fatigue; headache; parotid swelling; a pecia. *Withdrawal Symptoms*—Though these are not indicative addiction, abrupt cessation of treatment after prolonged therapy m produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restle ness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperact reflexes, tachycardia, ECG evidence of impaired conduction, sho congestive heart failure, stupor, coma, and CNS stimulation w convulsions followed by respiratory depression. Deaths ha occurred with drugs of this class. No specific antidote is kno general supportive measures are indicated, with gastric lavage.

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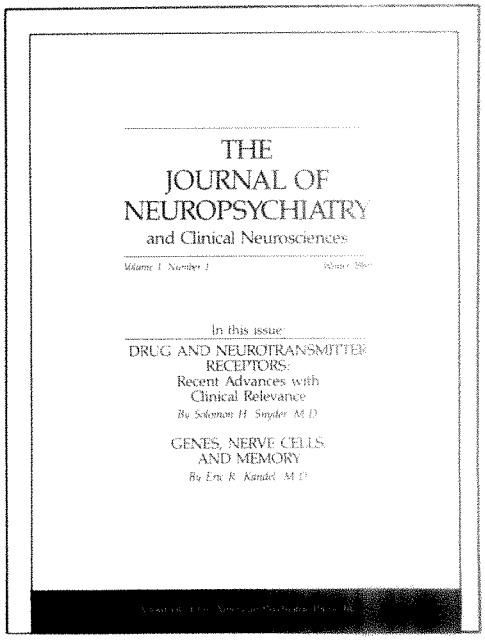
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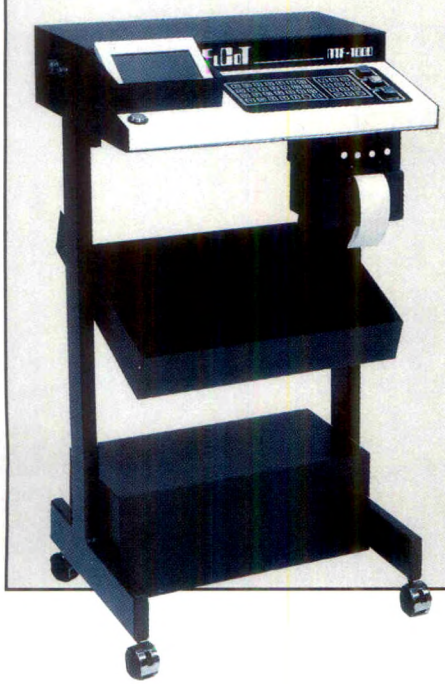
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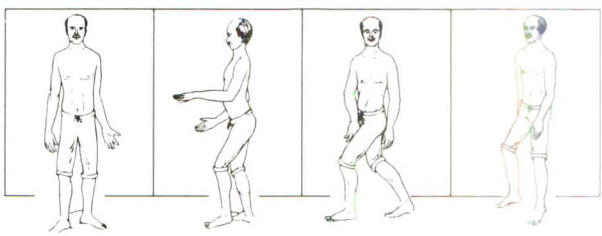
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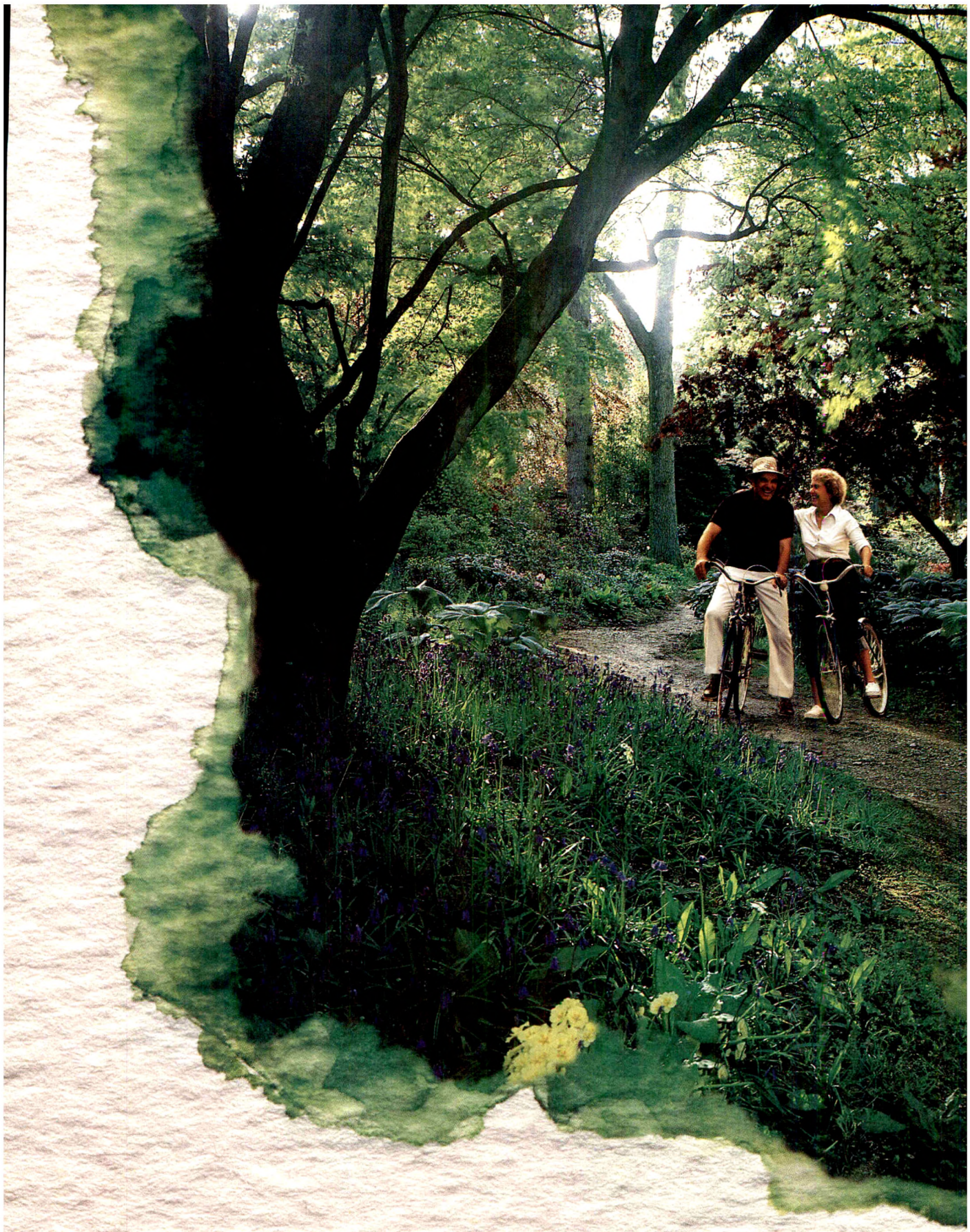
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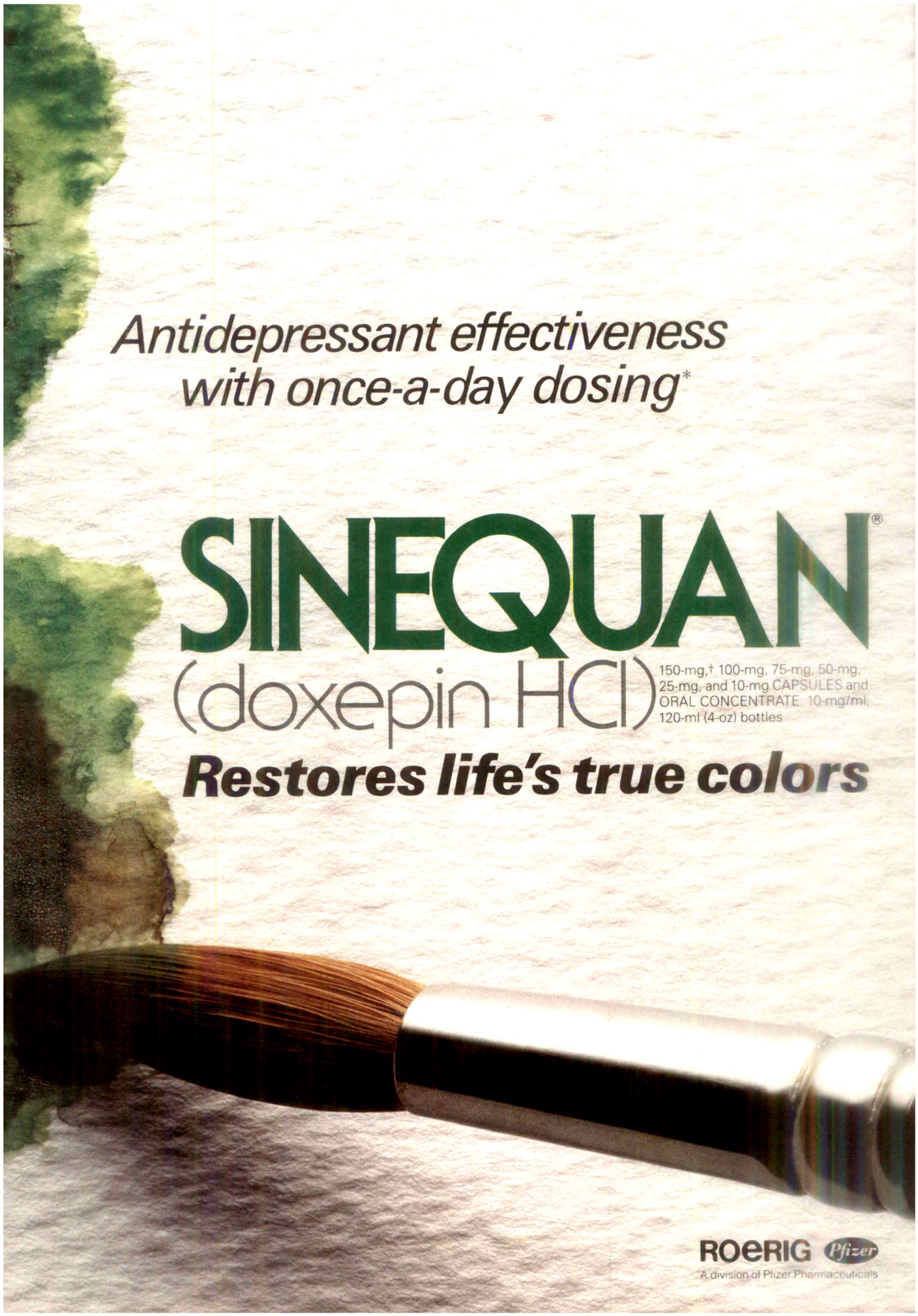


*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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SINEQUAN® (doxepin HCl)

BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate
Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.
A. Signs and Symptoms
1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment
1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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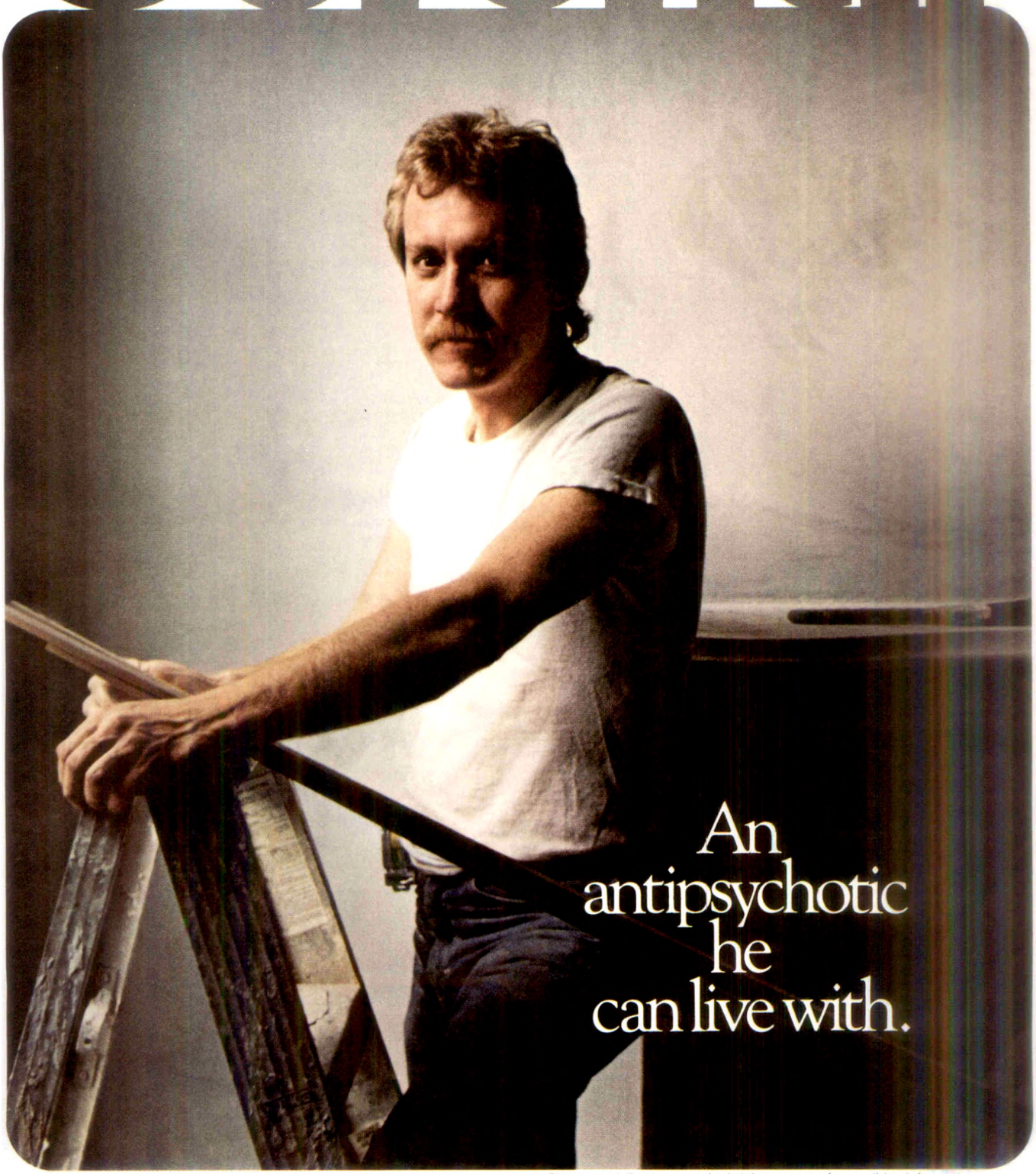
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(mesoridazine) Serentil®

as the besylate
IM/CONCENTRATE/TABLETS



Please see following page for brief summary of prescribing information

(mesoridazine) as the besylate

Serentil®

(mesoridazine) besylate tablets USP
(mesoridazine) besylate injection USP
(mesoridazine) besylate oral solution USP


Tablets: 10, 25, 50 and 100 mg


Concentrate: 25 mg/ml


Injectable 1 ml (25 mg)

Brief Summary of Prescribing Information

Contraindications: As with other phenothiazines, Serentil® (mesoridazine) is contraindicated in severe central nervous system depression or comatose states from any cause. Serentil is contraindicated in individuals who have previously shown hypersensitivity to the drug.

Precautions: While ocular changes have not to date been related to Serentil® (mesoridazine), one should be aware that such changes have been seen with other drugs of this class.

Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Serentil. Since convulsive seizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen while receiving Serentil.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis, the available evidence is considered too limited to be conclusive at this time.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness 1) that is known to respond to neuroleptic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the section on Adverse Reactions).

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Where patients are participating in activities requiring complete mental alertness (e.g. driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

Usage in Pregnancy: The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

Usage in Children: The use of Serentil (mesoridazine) in children under 12 years of age is not recommended, because safe conditions for its use have not been established.

Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.

Adverse Reactions: Drowsiness and hypotension were the most prevalent side effects encountered. Side effects tended to reach their maximum level of severity early with the exception of a few (rigidity and motoric effects) which occurred later in therapy. With the exceptions of tremor and rigidity, adverse reactions were generally found among those patients who received relatively high doses early in treatment. Clinical data showed no tendency for the investigators to terminate treatment because of side effects. Serentil® (mesoridazine) has demonstrated a remarkably low incidence of adverse reactions when compared with other phenothiazine compounds.

Central Nervous System: Drowsiness, Parkinson's syndrome, dizziness, weakness, tremor, restlessness, ataxia, dystonia, rigidity, slurring, akathisia, motoric reactions (opisthotonos) have been reported.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and blurred vision have occurred in some instances.

Genitourinary System: Inhibition of ejaculation, impotence, enuresis, incontinence have been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Cardiovascular System: Hypotension and tachycardia have been reported. EKG changes have occurred in some instances (see Phenothiazine Derivatives: Cardiovascular Effects).

Phenothiazine Derivatives: It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, biliary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram, including prolongation of the Q-T interval, lowering and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving the phenothiazine tranquilizers, including Serentil® (mesoridazine). To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, it should be noted that sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing characteristic electrocardiographic changes while taking the drug. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. Hypotension, rarely resulting in cardiac arrest, has been noted.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the **Warnings** section and below.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g. protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for neuroleptic drugs may mask the signs of the syndrome.

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

How Supplied:

Tablets 10 mg, 25 mg, 50 mg, and 100 mg mesoridazine (as the besylate). Bottles of 100.

Ampuls: 1 ml (25 mg mesoridazine (as the besylate)). Boxes of 20.

Concentrate: Contains 25 mg mesoridazine (as the besylate) per ml, alcohol, USP, 0.61% by volume. Immediate containers: Amber glass bottles of 4 fl oz (118 ml) packaged in cartons of 12 bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg and 50 mg of mesoridazine (as the besylate).

Consult package insert before prescribing.

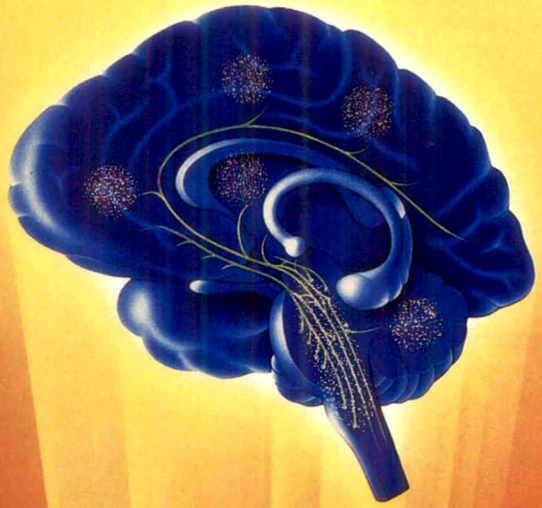
SE-BPI-6/87

Boehringer Ingelheim
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

SE-3459R

An antidepressant chemically unrelated to all other available therapy

PROZAC®
fluoxetine hydrochlorid



The first highly potent blocker of serotonin uptake

Prozac, unlike the tricyclic antidepressants, is targeted *specifically* at serotonin uptake. Its minimal action o other neurotransmitters may explain its favorable side-effect profile

Fewer side effects to disrupt therapy

Side effects with Prozac are generally mild and manageable and include nausea, anxiety/nervousness, insomnia and drowsiness

Use of MAO inhibitors concomitantly or in proximity to Prozac should be avoided

Rash and/or urticaria occurred in 4% of clinical trial patients

Wide margin of safety

20-mg Pulvule® once a day for depression

See reverse side for brief summary of prescribing information.

DISTA

Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285

Prozac®
fluoxetine hydrochloride

Brief Summary. Consult the package insert for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindications: None known.

Warnings: *Monoamine Oxidase Inhibitors*—Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General*—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of Prozac-treated patients compared to 4% of placebo and 3% of tricyclic-antidepressant-treated patients. However, only rarely have Prozac patients been discontinued for weight loss.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Life of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. (*See* Clinical Pharmacology and Dosage and Administration sections).

Use in Patients With Concomitant Illness—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 753 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

- Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.
- Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.
- Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breast feeding an infant.
- Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests—There are no specific laboratory tests recommended.

Drug Interactions—Tryptophan—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors—*See* Warnings.

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients.

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children—Safety and effectiveness in children have not been studied.

Use in the Elderly—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Adverse Reactions: *Commonly Observed*—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials—Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac—During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 Prozac-exposed individuals who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole—*Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System—*Infrequent:* angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block (first-degree), bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—*Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, and thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N=1,730)	Placebo (N=799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	—
Light-headedness	1.6	—
Concentration, decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4

Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N=1,730)	Placebo (N=799)
Body as a Whole		
Asthenia	4.4	1.5
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	—
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.8
Flu-like syndrome	2.8	1.5
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.4
Dyspnea	1.4	—
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.1
Musculoskeletal		
Pain, back	2.0	2.1
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.1
Sexual dysfunction	1.9	—
Frequent micturition	1.6	—
Urinary tract infection	1.2	—
Special Senses		
Vision disturbance	2.8	1.8

*Events reported by at least 1% of Prozac patients are included
— Incidence less than 1%.

Endocrine System—*Infrequent:* hypothyroidism; *Rare:* goiter and hyp
thyroidism.

Hemic and Lymphatic System—*Infrequent:* anemia and lymphadeno
athy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, ly
phocytosis, petechia, purpura, sedimentation rate increased, and thror
bocythemia.

Metabolic and Nutritional—*Frequent:* weight loss; *Infrequent:* gen
alized edema, hypoglycemia, peripheral edema, and weight gain; *Rar*
dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipem
hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficien
anemia.

Musculoskeletal System—*Infrequent:* arthritis, bone pain, bursit
tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystroph
muscle hemorrhage, myositis, osteoporosis, pathological fracture, a
rheumatoid arthritis.

Nervous System—*Frequent:* abnormal dreams and agitation. *Infr
quent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apath
ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusior
depersonalization, emotional lability, euphoria, hallucinations, hostili
hyperkinesia, hypesthesia, incoordination, libido increased, manic rea
tion, neuralgia, neuropathy, paranoid reaction, psychosis, and vertig
Rare: abnormal electroencephalogram, antisocial reaction, chronic bra
syndrome, circumoral paresthesia, CNS depression, coma, dysarthr
dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, r
stagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System—*Frequent:* bronchitis, rhinitis, and yawn; *Infr
quent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Rar*
apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibros
alveolitis, and pleural effusion.

Skin and Appendages—*Infrequent:* acne, alopecia, contact dermatit
dry skin, herpes simplex, maculopapular rash, and urticaria; *Rar*
eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutis
psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, sk
hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—*Infrequent:* amblyopia, conjunctivitis, ear pain, e
pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract
corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, pt
sis, strabismus, and taste loss.

Urogenital System—*Infrequent:* abnormal ejaculation, amenorrhe
breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhe
menopause, menorrhagia, ovarian disorder, urinary incontinence, urina
retention, urinary urgency, urination impaired, and vaginitis; *Rare:* abo
tion, albuminuria, breast enlargement, dyspareunia, epididymitis, fema
lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagi
orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, ur
thritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uteri
spasm, and vaginal hemorrhage.

Overdosage: *Human Experience*—As of December 1987, there were tw
deaths among approximately 38 reports of acute overdose with fluoxetin
either alone or in combination with other drugs and/or alcohol. One dea
involved a combined overdose with approximately 1,800 mg of fluoxeti
and an undetermined amount of maprotiline. Plasma concentrations
fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respectively.
second death involved three drugs yielding plasma concentrations
follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.8
mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine exper
enced two grand mal seizures that remitted spontaneously without specif
anticonvulsant treatment (*see* Management subsection). The actu
amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving high
fluoxetine doses. Other prominent symptoms of overdose included agit
tion, restlessness, hypomania, and other signs of CNS excitation. Exce
for the two deaths noted above, all other overdose cases recovered witho
residua.

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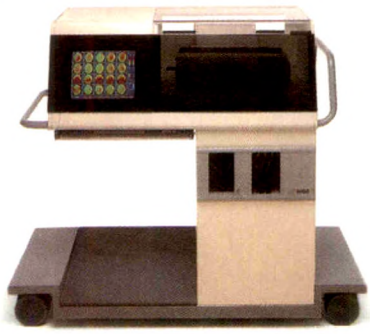
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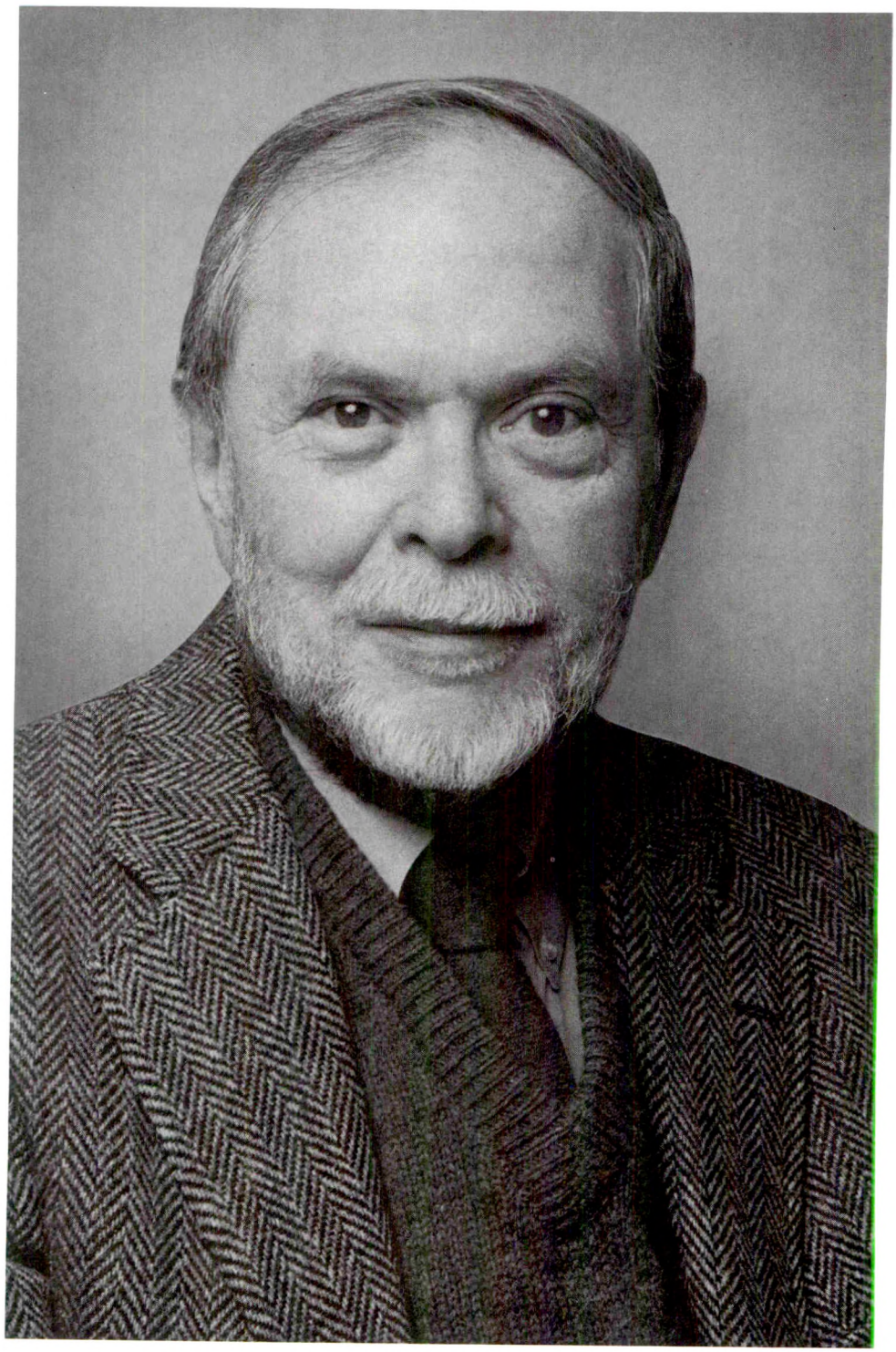
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Presidential Papers: 1988

1055 Presidential Address: Landfalls, Journeys, and Departures
George H. Pollock

1061 Response to the Presidential Address:
Is "Biopsychosocial" the Psychiatric Shibboleth?
Paul J. Fink

1068 George H. Pollock, M.D., Ph.D., One Hundred Sixteenth President, 1987–1988
Melvin Sabshin



George H. Pollock, M.D., Ph.D.

THE AMERICAN JOURNAL OF PSYCHIATRY

Presidential Address: Landfalls, Journeys, and Departures

George H. Pollock, M.D., Ph.D.

It has been a privilege to have been given the opportunity—one of the most important opportunities in American and world medicine—to work with and for you as your President this past year. Having been your Treasurer for 6 years before being your President-Elect, and now President, has given me 8 years of education in our Association. I have grown up and learned from our leaders, our members, and our colleagues in other branches of medicine and in other disciplines, and I appreciate what they have taught me and how I have been able to best serve you and our profession. I have the deepest of beliefs that our Association speaks for our specialty and our profession. We have addressed the challenges that face us, and I have the highest of hopes that we will continue to achieve our hallmark of excellence. Our Association plays a central role in medicine and in the mental health and illness disciplines. We have an identity that is a model for other groups. We can and do inspire younger colleagues, and this inspiration is virtually unequaled in almost any other specialty. We preserve what is proven and valuable; we continually seek new opportunities for excellence and strength in education, research, clinical service, and administration; we strive to protect the rights of the many who benefit from our advocacy—and we benefit from working with them. People matter to us—our patients, our colleagues, our families, and ourselves. The dimensions of this statement—"people matter to us"—are essential to our work. But more of this shortly.

Joseph Conrad opened his 1906 autobiographical memoir, *The Mirror of the Sea*, by stating, "Landfall and Departure mark the rhythmical swing of a seaman's life and of a ship's career. From land to land is the most concise definition of a ship's earthly state" (1, p. 1). Arrivals and departures are personal. It is not the ship that takes its departure; it is the sea captain, the officers, and the crew who are involved in the arrivals and the departures. The ship, as long as it is safe and secure, carries on; but the people who run the ship come aboard and then take leave.

These past 2 years have been filled with many landfalls and departures for me. I have visited many places and met and came to know many people; I have been exposed to many ideas and have come into contact with various dilemmas, concerns, and resolutions. My education, my perspectives, my knowledge, and, I hope, my wisdom have been increased. Like a sailor, I have been on many voyages. I wish I had the time to share with you all that I have seen and learned; but while this is not possible, I do want you to come on several trips with me. We will stop at a few ports, exploring what our relatively tight schedule will allow. I do hope that the few places to which we sojourn will be of value and interest and will stimulate a revisiting.

THE NATURE OF WORK

Our first port of call actually is a revisiting. In my address to you last year I talked about the nature of a profession and how this relates to the nature of work (2). I wish to now examine this further.

Work is an enormously complex activity, having its origins in infancy. It deals with such issues as mastery, competency, learning, identification, skills, thinking, and doing. As development proceeds, we become aware of the various factors that play a role in comprehending work, its discontents, and its satisfactions. The relationship of play in work and work in play is well known to adults as well as to children. Indeed,

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even though work is considered a central human activity, it is found also in the insect and animal kingdoms. The transformation of raw materials or ideas into more refined products such as things or theories, and the role of such physical and mental changes in this work process, have many different meanings for man. It can offer a sense of accomplishment or meaninglessness, and so be a source of pride or shame. The study of the evolution and the nature of work itself, including the pathologies of work, will be of importance in our world as changes in economics play an ever increasing role in our lives. Issues such as economic security, inflation, national debts, financial support of teaching and research, and reimbursement for services already concern us. An automated society with its accelerated demands for highly trained technicians, scientists, professionals, and other workers will alter the terrain of life as we know it. The changing status of women, minority groups, and the handicapped should alert us to more alterations in the status quo.

Throughout history, work and labor have been linked with the provision of goods and services essential to the maintenance of human life and welfare. This struggle for maintenance touches on such issues as poverty and starvation, and, hopefully, on the economic rewards attached to occupations as well. Unemployment is frequently the end product of an income reduction process and causes great concern. Fees and compensation are part of maintenance and reward. This compensation not only is economic but includes self-esteem, power, and control dimensions as well as play-satisfaction-gratification rewards. Thus we have external as well as internal dimensions to work. The power and ability to determine the intensity and duration of work and the manner in which work is divided and allocated, and the decision about what work is or is not to be done, who does the work, and who receives its rewards, are also critical. These considerations introduce the question of elites who are the determiners of decisions and issues of power and control.

Let us look at the division of labor in the work situation. As Rinehart has noted, the most important divisions of labor are specialization and the separation of mental and manual labor. "Specialization is a twofold process which entails a fragmentation of work into minute tasks and the permanent assignment of these tasks to specific individuals" (3, p. 21). Preindustrial labor was much less divided and detailed. Farm and small-town workers were multifaceted in the tasks and operations that they could perform with efficiency. The general practitioner, to bring my statements closer to home, was a resourceful jack-of-all-branches-of-medicine, and specializations then were qualities of general skills and knowledge. Independent workers could still set the pace, direction, and focus of their work. Task orientation, and not time, was significant, and compensation for labor was not geared to the clock. Gradually, labor became more specialized, less personal, more technical and functional, and more factory-corporate organized for profit. Worker autonomy decreased and tension and concerns increased. Today we find that a more recent development is the individual professional workers who are self-incorporated or working for a corporation as employees.

In regard to medicine, here, too, we have been and are in the midst of an industrial revolution. Since psychiatry is a subdivision of the division of labor called medicine, we are involved in this process with all of its threats and disadvantages, as well as its positives. We may be in the process of transforming the professional class into the new working class, and this transformation may evoke alienations and threats. In any event, there seem to be unrest and fear with uncertainty about who makes decisions and who controls what, where, and how. With the increasing size of the health-illness industry, the business activity becomes further subdivided, and the control by administrators and managers who are not health-illness professionals creates more tension. When there is a surplus of workers, the market conditions change, competitions increase, concerns over economic territoriality become manifest, and new organizations and coalitions (e.g., consumer groups, advocacy groups, and combined research groups) appear. New medical-industrial-university-hospital complexes are created, and they can further remove control of professional decisions from the individual practitioner.

OCCUPATION AND SPECIALIZATION

Let us now briefly visit the ports of occupation and specialization and make some observations. Although occupational licensing in America may control competition and diminish choices for the ordinary consumer, it can also protect the consumer by requiring quality services; and if these services are not delivered or are incompetently delivered, licensure can be removed or restricted for varying periods of time. Voluntary associations can set standards for work and membership qualities, and although these standards are different from licensure, which is the province of government, associations still exert a powerful force in controlling the conduct of their members. Professional associations, like trade unions, came into being as a result of the Industrial Revolution. Such associations have many different functions but, unlike licensure control, they do not exert nonvoluntary, external control of members but internal organizational control involving scientific, clinical, technical, legal, and ethical areas.

Professionals usually are individuals who by virtue of their education and experience are acknowledged to provide high-quality services to consumers. Our patients are our consumers, and we professionals are their service providers. What we do is work, and we have the problems of workers. We are in the midst of our own industrial revolution and we are trying through self-regulation, including provision of services at a fair price, to avoid more public control. As professionals, we usually do not think of our patients as

customers, although we now consider them as consumers. Now we frequently engage in marketing efforts much like those of other businesses; we are incorporated and so subject to the same laws as for-profit corporations; and economic affairs and public relations, although called by other names, are some of our undertakings. (We now are allowed to advertise for customers.) We also have trade associations and lobbyists. So I ask, as have others, what are the differences between professionals, and other occupations not so designated, and workers?

Professionalism, unless it can clearly define its distinctive character, may take on a different meaning in the industrial world of our fields of work. Young has noted that

> Before industrialization only "learned" professionals—physicians, lawyers and clergy—were considered professionals. In the classic sense, then, barbers would not be considered professionals. Barbers do, however, display many attributes of professionalism as defined by sociologists, such as formal training programs, professional associations, the full-time nature of the occupation, and state licensing laws. (4, p. 3)

The learned professionals sell their services to customers in exchange for money. By and large, some—especially in our discipline—charge by the clock just as plumbers and mechanics do, and the marketplace determines many more aspects of our work than we may consciously consider. Economic forces determine many of our activities as well as those of our professional organization.

Let us look at the history of occupational licensing, which is comprehensively discussed in Young's book on this topic (4). Regulation of the professions was found in ancient Babylon and the Code of Hammurabi. Young notes that the Code, written about 1800 B.C., set predetermined fees for surgeons' services—shades of today!—and set malpractice penalties, e.g., the severing of the surgeon's hand if the patient died as the result of an operation—a bit more severe than malpractice penalties today, but perhaps some surgeons would disagree with me. The first licensing law similar to modern laws came from thirteenth-century Sicily when all medical practitioners had to be licensed, and fee schedules and ethical codes were established. In the next century similar laws were enacted in Spain, Germany, and mainland Italy. Early guilds required membership of all who chose to practice a given trade or craft, thus creating a monopoly. Competition was restricted and limits were imposed on the number of apprentices who could enter a trade. English guilds controlled prices and quality standards. However, the Industrial Revolution ended this guild control.

The guild system in Europe began to deteriorate at the time the first American colonies were established, and therefore this system never took hold here. In 1639, the first law regulating a profession in America—the control of physicians' fees—was enacted in Virginia, and 10 years later a law to control the quality of medical services was enacted in Massachusetts. Subsequently, many state licensing laws were not passed or were repealed because of opposition to state regulation of the medical profession. By the mid-1800s the medical profession was open to anyone who chose to call himself a physician. This led to the formation of the American Medical Association in 1847, whose purpose was to have

> a powerful professional organization that would lobby for the interests of "responsible" practitioners—in short, tough licensing laws that would force poorly trained physicians out of the profession and provide a measure of economic security to those who remained. Although the AMA met with considerable resistance at first, its efforts eventually were resoundingly successful. By 1900 every state had enacted a mandatory licensing law. (4, p. 12)

Occupational licensing, federally or state regulated in the United States, has as its principal justification the protection of the public, i.e., protection of public health, consumers, morals, and safety. Those who prove to be incompetent, immoral, or a threat to personal and public safety can have their licenses revoked. In this way licensure could be considered as an insurance of good care for the public. The more current requirement of continuing, regular relicensure is designed to protect the public on an ongoing basis from practitioners who should not be allowed to practice. The impact of licensure on the scope of professional practice and its relation to specialization has resulted in

> the tendency of all professions to define as broadly as possible what practice is restricted to licensees. Licensing laws are often called "practice acts," because they grant authority to licensees to engage in certain practices within a profession. Once the scope of practice is established by law, it is illegal for anyone without a license to perform any of the activities covered by the law. (4, p. 81)

There are now "turf" battles occurring in many disciplines. For example, lawyers have fought accountants over the right to give tax advice, with the argument that such service constitutes the practice of law. Now some tensions exist between lawyers and real estate brokers concerning jurisdiction over contracts. Similarly, in medicine we have seen many turf disputes. The protectionism of licensure is under constant scrutiny, especially as costs escalate and paraprofessionals are used to reduce these costs. At times the battles end in court, and there have been instances in which the judicial decisions involve therapeutic programs, an area of tension and concern to some. The legislative branches, especially in the states, will be more involved in issues of the scope of licensure in the future. The call for clearer boundaries will be a necessity. Sunset and sunrise laws with regard to licensure are already present, as are relicensure requirements. High standards, cost reduction, more availability of quality care, greater personal involvement—all are the goals of our

profession. The challenges are there now. We must address them thoughtfully, carefully, and wisely.

The independent professions are likely to come under attack. Lord Hailsham recently expressed the point of view that the basis for these attacks may well lie in competition, dislike of restrictions, and monopolistic practices. He wrote, "my own profession of the law will be in the forefront of the battle" (5, p. 17). His focus is on the professions of law, accountancy, engineering, medicine, dentistry, nursing, architecture, and ancillary professions. "The existence of independent and learned professions is one of the hallmarks and glories of a free society" (5, p. 17). Yet such self-employed suppliers of services to the public should not be immune from public scrutiny and, when necessary, criticism. Incompetency, negligence, dishonesty, unnecessary monopolies, and undesirable restrictive practices only do harm if covered up, and therefore self-control and self-regulation are essential. Lord Hailsham affirms that to practice competently in any profession, long periods of study and vocational training are required. "The minimum or adequate standards of competence or professional skill are not easily defined at any given time, except by those who themselves are members of the profession, and these standards constantly vary in the light of growing scientific and technical knowledge" (5, p. 18). We must define, study, examine, and refine our standards constantly; otherwise, others who may be less qualified will do this for us, and we will feel the impact of our neglect.

These issues confront all of the professions today. Perhaps there should be interprofessional meetings in which these matters can be discussed for the benefit of all professions and, more significantly, for the benefit of the public. It may then be possible to work collaboratively with government bodies for the additional welfare of the public. Scholarship, experience, and skill have unique features for each profession and its specialties, but there are at times overlooked common goals, values, and dilemmas that can be shared.

We cannot be arrogant in the face of consumers who are knowledgeable, alert, and appreciative of the specialist's skill and knowledge, but are not in awe of it. We must be responsive to people who seek our care in ways that gain their confidence and trust. Technical skill may not be enough! As I said previously, the consumer movement has come to medical care and medical research. While this development is new for our discipline, it can be most helpful to us, even though it also presents new aspects of the issue of control of our profession. Patients and their families are our partners—our helpers—and our vigilant scrutinizers. But we have other partners as well—business and industry, insurers, and medical corporations. This is a period of pressures, tensions, and stress. But again, if we see these as opportunities to demystify our profession, we will gain allies instead of adversaries.

Change is here; if we do not embrace it, then we will have to chase it. There are new boundaries, new models, new disciplines, and new educational and career paths. In this time of transition there is a sense of crisis and confusion. Our younger colleagues are looking for role models, and some of our role models are themselves looking for their own identities. Yet, again, these are challenges as well as opportunities.

Reality and credibility are components of authenticity. If we are authentic, we must present ourselves as such—not defensively, not offensively, but realistically and with forthright assertion about who we are, what we do, how we are unique, who we serve, what is our education, what are our experiences, what are our traditions, and what has been, is, and will be our role in society. Let us examine our responsibilities and accountabilities to our patients, our colleagues, and our students and monitor ourselves—in ethics, standards, and quality of care. These are some of the components of our professional identity.

I realize that time moves on, and we have to leave this port, for there is another stop on this trip before we come to our resting harbor.

DUALISM IN PSYCHIATRY

Switching to another theme, I will now quite briefly address the topic of dualism in psychiatry. In his 1882 Rede Lecture at Cambridge, Matthew Arnold made an impassioned defense of humanistic education against those who urged a predominantly scientific curriculum. Arnold argued that "Most people needed art and poetry, religion and philosophy . . . for the realization of their true humanity" (cited in Himmelfarb [6, p. 85]).

In 1959, C.P. Snow (7) also delivered a Rede Lecture, "The Two Cultures," in which he decried the gulf separating the scientific and humanistic cultures. In 1963 (7), Snow revised his earlier presentation and called the new essay "The Two Cultures: A Second Look."

Gertrude Himmelfarb, a distinguished historian, argued that "It is not science and social science that are the antagonists in the Two Cultures debate, but science and the humanities" (6, p. 89). She wrote, "The social sciences are all too easily 'scientized' " (6, p. 89). Even in the humanities, political philosophy seeks to transform itself into political science, history into social science, literary criticism into semiotics, and theology into semantics. The effect has been to "deconstruct" those disciplines and to desocialize, dehumanize, and demoralize them by removing their recognizable social and human reality.

The latest phase of the more than century-old debate about the two cultures seeks "to unite the Two Cultures analytically and linguistically, to create a language of discourse so recondite and internal, so concerned with the mode of discourse itself, that other modes of experience . . . are but dimly perceived as through a glass darkly" (6, p. 93). Himmelfarb's prediction may be correct concerning the one or two cultures' tasks to interpret reality. In any event, the two-culture debate is related to the dilemma we see in

psychiatry today—mind and brain are not the same. Each should be studied and worked with independently. Each will make its contribution to our understanding of humankind—his or her ills, his or her health. A synthesis may occur in the future, but for the present let us not attempt such a merger prematurely. Snow, in his earlier lecture, noted that the only way out of the dialectic or dichotomy is to rethink our education, which he believes is too specialized (7). He indicates that specialization is increasing and so the gulf will increase. We have seen evidence of this in our own specialty.

The problems of mind versus body, the Cartesian dualism, innate versus environment have been with us for some time. We want to know and do know more about mind, brain, body, genetics, the interacting variables throughout the life course. With about one-third of our population over the age of 50, we need new studies and new data on normality and pathology in the later third of the lifespan.

Some of what seemed revolutionary in the past now seems like a statement of orthodoxy. The flow of ideas and research can and does stimulate new revolutions in thought, experimentation, clinical approaches, and service delivery systems. Where are we as a specialty in this increasing fortissimo of change? Are we in danger of concentrating our efforts in defensive rear-guard activities? Or can we be in front and at the crest of the wave? Do we have two cultures in psychiatry that are separate but linked, as are the right and left lobes of the cerebral hemispheres? Do we have a right-brain psychiatry and a left-brain psychiatry, i.e., a focus on meaning-aesthetics-emotions and a focus on mechanism-structure-molecular functioning? Does the present climate of delivery system tensions and increased legislative-economic and judicial involvement in our field change or divert us from our professional missions and goals? This is a time of order and disorder, entropy and control, chaos and regulation. Can we take innovative, creative, and revolutionary steps to resolve some of the issues that otherwise drain our energies and resources and thus make them less available for investment in our future development?

I believe we can shift some in our positions—our directions. It is not easy, especially since change results in anxiety, resistance, mourning for the old, and a form of stigmatization of the advocates of new approaches and new ideas. For example, what if we created a membership class in our Association for physicians who are not psychiatrists, and for nurses, in order to familiarize them with what we do? Or, to be even more bold, what if we had a class of membership for psychologists and social workers, with whom we share some common concerns and interests? Are we prepared to try or at least to think of a different path without incurring the wrath of our colleagues? Yes—I believe we can think of this. In dreams, sometimes new realities appear. Dualisms and pluralisms can be useful, but if they restrain our efforts or wastefully deploy our energies, they are counterproductive. No single approach tells us the whole truth, and yet multiple approaches that are competitive with each other can be destructive. Symbiotic ties in research, teaching, practice, and administration may hold more promise. To paraphrase Winston Churchill, we shape our structures but must be aware of the fact that afterwards these structures, which may be outdated, can shape us.

There seem to be two cultures in the mental illness disciplines today. One emphasizes the statistical, factual, controlled study—and is relatively impersonal. The other culture is closer to the less precise, less easily quantifiable social science-humanities axis. Each has its own research methods, method of data collection, data interpretation, and data analysis; each uses some degree of metaphor-symbolism; each has some degree of personal involvement and uses the self as part of the research process. And yet there are differences that cannot be ignored. If scientific method is reality testing, we can say that each uses this method and yet there are differences. We are all part of psychiatry, but do we have a dualism that should be acknowledged without avoiding possibilities of attaining articulations of unity? This, too, is a challenge that we face.

Objectivity, detachment, dispassionate study, and skepticism are all useful and needed in research, but they can cloak involvement with human beings. Objectivity can mask a noncaring attitude. On the other hand, excessive sentimentality and overidentification with those who need our services can have adverse effects. As human beings we admire culture, political freedom, truth, personal integrity, and broad-based education while seeking the highest technical competence and seeing ourselves and our discipline in the broad framework in which we live, work, plan, and, hopefully, enjoy life. We must ask ourselves what are the limits of our responsibilities as clinicians, researchers, and teachers. We cannot cover all fronts, but we can affirm our commitment to the betterment of humankind and the human condition. These are our overall ideals and goals.

Roger Sperry (8) has written a book on *Science and Moral Priority: Merging Mind, Brain, and Human Values*. In this volume, dedicated "to those many generations hopefully to come," Sperry, a Nobel prize winner, neurobiologist, and pioneer brain researcher, emphasized that values are the number one problem of our times. He bridged science and values and mind-brain interactions and argued for a union of science with ethics and religion. We can challenge the Cartesian dualism as it has manifested itself and, in some academic and clinical settings, still manifests itself. We can espouse and work toward a unitary holistic model that is in accord with our professional reality. Ultimately, I believe we will not have dualism.

CONCLUSION

I realize that, without our being aware of it, our ship moved from one port of call to another and is now

quietly moored in its harbor. I have not provided solutions; instead, I posed problems that may help us in our quest for answers. Psychiatry is a caring profession and not merely the end user of technology. It is like a huge ocean liner, sailing under one name, but with many different decks. There is a shared engine room, heating plant, electrical system, and basic external structure—yet the decks may be different in terms of space configuration, content, and decorating scheme. All the decks are separated, and yet they are linked by common stairways. And each of those on board, although a separate passenger and unique individual, does see, meet, and talk with the others who share the same basic concerns and needs during the voyage and, ultimately, the same hoped-for destination.

Thank you again for letting me take the journey I have taken on your behalf and for our patients.

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Response to the Presidential Address: Is "Biopsychosocial" the Psychiatric Shibboleth?

Paul J. Fink, M.D.

The word "shibboleth" means "useless term" and was a neologism used as a password in the biblical story of the Gileadites versus the Ephraimites. The latter could not pronounce an "sh" and therefore said "sibboleth" rather than "shibboleth." In this original context the term "shibboleth" took on a special importance as a password despite its "meaninglessness." Since then, this original sense has been displayed by the connotation of shibboleth as empty jargon. The risk of this type of decay toward meaninglessness, a conceptual and verbal entropy, remains as present a risk for us and our scientific concepts and formulations as it was for our forefathers of biblical times. A clear example of this has been the gradual loss of meaning that has followed the original power of the term "biopsychosocial." In 1977, George Engel's paper on the topic of a new approach to medicine that used the biopsychosocial framework rather than biomedical reductionism appeared in *Science* (1). His ideas were a challenge that seemingly went unnoticed in the world of medicine and surgery but immediately attracted attention in psychiatry. Since we believed we were already using a biopsychosocial paradigm, and since we were trying to preserve the art of medicine in the midst of a potentially dehumanizing scientific and technological explosion, and since we had constantly been involved with the sociocultural aspect for a patient's illness and rehabilitation, it seemed natural for psychiatry to grab on to the biopsychosocial paradigm as a natural synthesizing model for modern, forward-looking psychiatry. This was even more so because Engel, although not a psychiatrist, is one of the heroes of our field and one of the fathers of the theory and practice of consultation-liaison psychiatry.

This makes it seem more unfortunate that the term "biopsychosocial" has become an intellectualized, overused shibboleth (password) in psychiatry and is destined to follow the fate of such other hollow terms as "eclectic" and "mental health," which have lost their power as metaphors.

In this paper I will review the work of George Engel and Morton Reiser and then develop the clinical, educational, and research applications of the biopsychosocial hypothesis. I will discuss, in addition, how the concept will help unify the mental health field. Recent presidential themes have alluded to the issue that I address: Carol Nadelson's "Unity Amidst Diversity: Future Challenges" (2) and George Pollock's "Opportunities and Challenges That Confront Medicine and Its Specialties, With Special Reference to Psychiatry" (3). Both focus on our pressing need to integrate the many factions of contemporary psychiatry. If we in psychiatry were able to take biopsychosocial seriously and incorporate it, conceptually and practically, into our clinical approaches, our research efforts, and our systems development such that our profession could be unified and strengthened by a synthesizing process which would be championed by all psychiatrists, regardless of specialty interest, clinical approach, or research focus, we would make large strides toward the unification of our field. We might, in short, by revitalizing Engel's original concept, solve one of the most vexing problems facing American psychiatry today.

THE BIOPSYCHOSOCIAL PARADIGM

This issue was poignantly called to my attention recently while I was doing grand rounds in a university setting. A schizophrenic patient's history was presented, and it fell neatly into three areas of interest: 1) the biological nature of the disease with relentless recurrence, the failure of the staff to find the "right" drug regimen, and the side effects to drugs shown by the patient; 2) the patient's peculiar, unique hallucinations, delusions, and supersensitivity to fantasies that were so strangely and yet understandably related to his early and recent life experiences; and 3) the chaotic home environment and sociocultural milieu from which the patient was brought to the hospital and to which he seemed destined to return. In my discussion, I did not focus on any one of these important clinical areas but on all three, weaving the theory and clinical advice into a biopsychosocial fabric that challenged

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the room full of residents to examine not only this patient, but all patients, from a multidimensional point of view. As I left the hall, I thought that when I was a resident we had to do dynamic formulations on all patients; perhaps now, 30 years later, we might require biopsychosocial formulations on all charts.

Breakdown of the biopsychosocial paradigm into one of its component parts, however, is more the rule than the exception. In his recent address to the American College of Psychiatrists, Alan Stone addressed the extreme position taken by Gerald Klerman, a renowned psychiatric researcher, who advised that efficacy ought to be the standard for malpractice and, by extrapolation, all psychoanalysis was malpractice because there were no good efficacy studies of the procedure. Such a view, even from the important position of the devil's advocate, is the antithesis of a biopsychosocial perspective and divides the field into its three seemingly unrelated parts: bio, psycho, and social. Is it possible that the sum is greater than its parts? The 1950s were a decade in which psychoanalysis dominated the field. In the 1960s behaviorism and community mental health held sway. In the 1970s neurobiology was king. In the 1980s we began the healing and synthesizing process, or have we? Are we truly training residents to be multidimensional, biopsychosocial thinkers, feelers, researchers, and clinicians, or are we pretending to do so, covering up our separate and biased selves with a soothing biopsychosocial shibboleth?

This is not an issue of blame or fault, but in large measure a result of the explosion of knowledge in our field over the past two decades. Psychiatric training in each of the past decades has emphasized singular and new approaches to illness, and we have all felt the force of the new or current point of view in determining and directing the course of our future professional lives. Perhaps because of the challenge of mastering "the new," many of our brethren were neither interested nor bothered to learn and incorporate that which did not follow the emphasis of their original training, and many outright disapproved of growth in the field which went in directions contrary to their own interests. Residents of today must synthesize information from diverse sources. The explosion of knowledge in the past several decades continues, and the task of current trainees and practitioners is one of integration.

An exception to the myopic trend of the past decades is Thad Barringer, a clinician for 35 years and recent past president of the Southern Psychiatric Association. In his presidential address, he discussed six cases from his practice, three patients whom he treated in the 1960s and three in the 1980s. These matched cases were compared in terms of his own technique and the cost, in constant dollars. His growth and change in 25 years were obvious. He used techniques and procedures in the 1980s that were not even dreamed of in the 1960s, and his flexibility and sensitivity to the patients' needs were remarkable. In addition, the costs per patient were less and the therapeutic effects as good if not better. He was practicing biopsychosocial psychiatry at its best, but as he confessed, his continuing education required a wide open mind.

DEFINITION OF PSYCHIATRY

Recently, the Board of Trustees of the APA adopted a definition of a psychiatrist (4) that is built on the biopsychosocial concept. It reads as follows:

> Psychiatry is a medical specialty. A psychiatrist is a physician educated and trained to provide direct service, leadership, and responsibility for the diagnosis, treatment, and management of those who have disorders of behavior, thought, feeling, or action. He or she is specifically trained in the simultaneous relevance of biological, psychological, and social factors. Psychiatrists recognize that there are multiple etiological pathways to the development of symptoms. Referral for treatment and management occurs when needed.

There were those who objected to the definition because it was too broad; others said too narrow. Still others thought it unnecessary, and others felt it might be provocative to nonpsychiatrists' groups. Its utility lies most in its ability to rally all psychiatrists around the concept of biopsychosocial and in turn diminish dissension, bickering, fragmentation, and intraprofessional disrespect.

There will always be those whose interests and efforts will direct them to one of the three pillars—bio or psycho or social; whose research will be primarily in a narrow band; whose successful clinical work will be at one of the poles rather than at the center. These people will challenge the biopsychosocial establishment. In fact, now the majority rather than the minority seem to be at one pole or another. It is the people who adhere to one model, to the exclusion of all others, who make it difficult, if not impossible, for a true biopsychosocial ethos to pervade our profession.

But why is a biopsychosocial model important for psychiatry now? The issue is broader than psychiatry alone; it is a problem for all of medicine and concerns our place in the medical establishment. Engel's position concerning biopsychosocial was clearly not in defense of psychiatry, but a criticism of the approach of all medical care as reductionistic and biomedical. He is much less ambivalent than we when he says:

> That psychiatrists are physicians is a fact, not a question of definition or philosophy. Being a physician means that psychiatrists have been exposed to the same basic and clinical education as have other physicians and hence, have a broader and more extensive acquaintanceship with the biological dimensions of disease, illness, and treatment than do health professionals who are not physicians. The fact of physicianhood significantly influences how they view themselves as well as how they are viewed by the public and by society. Other professionals in health-related fields do not, and cannot, have the same self and public image as do physicians. (personal communication)

Systems theory as a paradigm was unable to influence either medicine or psychiatry sufficiently to move us beyond the continued reliance on the 17th century's scientific world view. Engel says, "for three centuries the natural science model, which provides the conceptual orientation for today's biomedical model, has excluded human issues from the scope of science, a reflection of the reductionism, mechanism, linear causality, and dualism characterizing its 17th century Newtonian-Cartesian origins" (in preparation).

NEW PARADIGMS NEEDED

Other areas of science have moved beyond a very narrow dependence on classical natural science in an effort to include the wide-breadth of human phenomena. A broad sense of scientific evidence supports the interdependence of psychosocial phenomenon and scientific observation. One cannot separate the person from his or her work, nor can one assume that the experience of the scientist is not built into the discovery and the use of scientific tools that make it possible for discovery to take place. John O. Beahrs has written a book entitled *Limits of Scientific Psychiatry: The Role of Uncertainty in Mental Health* (5). His book elucidates the uncertainty principle as inherent in all systems. In the foreword to Beahrs's book (6), Engel quotes Beahrs as saying that the uncertainty principle "has become a cornerstone of modern science, forcing physicists to abandon the strict, causal determinism of Newton and LaPlace, in deference to a reconceptualization in more fuzzy probabilistic terms." Building on quantum physics and theories of the wave particle dichotomization, Beahrs makes a connection between these physical findings and the many dichotomies that abound in mental life; "voluntary vs. involuntary, conscious vs. unconscious, dependence vs. autonomy" (5), etc. From our clinical work we recognize transference as the cornerstone of modern psychotherapy. We have carefully studied the movement back and forth between the patient and the doctor and have recognized the ubiquity of uncertainty on both sides. With this post-Cartesian world view, psychiatrists could open new vistas for medicine in exploring the clinical applications of the uncertainty principle.

Engel remarks, "a relational mode is required to deal with data in a uniquely human realm of articulated language, symbols, thoughts and feelings by means of which what we privately experience is organized and communicated and relationships established and managed. In this mode, dialogue serves to clarify the meaning and verify the information that is being reported" (7). For about 100 years, psychoanalysis has been attempting to bring meaning to human behavior that appears to be irrational or is difficult to understand in a unidimensional fashion. Engel goes on to say that communication with patients is the only means by which the doctor learns what is going on, whether the events are biochemical, physiological, psychological, or social. He says, "this is the process of clinical reasoning. It is a mode in which clarification of meaning and the establishment of veracity take precedence over measurement. By tradition the observational mode, as represented by the empirico-analytic approach, is accorded scientific status, while the relational mode, as dialogue, is not" (7). The following statement exemplifies how we use Engel's words to play a role in the incorporation of psychiatry as a full partner with our medical brethren—not because we are at the back end trying to get in, but because we are at the front end with knowledge and abilities well beyond that of the average doctor. Engel says:

> the physician has no alternative but to behave in a humane and empathic manner, that is, to understand and be understanding, if the patient is to be enabled to report clearly and fully. Only then can the physician proceed scientifically; to be humane and empathic is not merely a prescription for compassion, as medical educators would like us to believe; it is a requirement for scientific work in the clinical realm. (7)

Yet, despite the clarity of Engel's conceptions and their utility in clinical practice, we are slow to make them part of our medical world views. Doctors are uncomfortable with uncertainty. In fact, our entire system of medical education is constructed as if everything were certain. The fact that what is certain today will be obsolete tomorrow has little influence upon faculties, students, and curriculum committees throughout the United States. To quote Engel:

> by calling attention to the uncertainty inherent in mental operations, Beahrs takes a long step toward breaking this impasse. Once quantum physics had acknowledged the indispensability of mind and conceded its irreducibility to ultimate elementary particles, it also had to recognize the quality "entity" ascribed to phenomena in nature to be like time and space, also a mental construct and not a true representation of natural processes. In nature what are in fact continua, or at least connected, acquire by mental operation sharp boundaries . . . . After all, a completely determinate mental apparatus, like some programmed robotic machine, would, in fact, be totally inadequate for life's tasks. (6)

Willingness to move and change paradigms is the single most important part of how the biopsychosocial model will affect the greater realm of medicine and psychiatry. It, too, will be supplanted by other paradigms that capture the imagination and inform science, that further expand and integrate our understanding of human functioning: how people operate psychologically, how they fit into their society, and how their biologic makeups affect their mental life. An interesting new paradigm that goes beyond biopsychosocial in its terminology and its approach is described by Foss and Rothenberg in a new book called, *The Second Medical Revolution* (8). In this volume, they indicate that détente, in their terms, "the joining together of biomedical cure and holistic care, did not work. Such

an approach, in any guise, is conceptually confused. It asks that we simultaneously accept the patient as a biocultural being at one level and a physiological complex organism at the other" (8). They have developed the "infomedical model," which begins with the assumption that the human patient is such an ideal decoder—a cybernetic system whose state of health (or illness) is the product of both its internal organization and external messages that may derive from a variety of levels of organization, e.g., physical, psychological, or social.

By moving to an information model, they begin to use messages as the metaphor. Thus, in their book, they talk about bio-messages, which are physical, psycho-messages and socio-messages as well. They add techno-messages and programs. Realizing that we are inventing new ways to destroy the body, mind, and culture, they now have broadened the sphere of understanding beyond the informational levels of biopsychosocial. It is refreshing to know that there is a growing body of literature which sees medicine in its reductionistic, biomedical approach as a death knell of modern medicine and not something that we in psychiatry should, willy-nilly, be chasing after and imitating. Thus, rather than neglecting the strength of our own world view, the biopsychosocial approach, or perhaps if Engel, himself, is ready to move on to a new paradigm, we might join Foss and Rothenberg in the infomedicine paradigm.

There are risks to our not adopting a broad-based approach. Historically, we are the humanizers of modern medicine and in some ways of modern society. However, because of our own ambivalence and our own inability to fully practice the biopsychosocial concept, we are quickly being replaced by laymen, self-help organizations, nonphysician mental health professionals, and others, who lay claim to a territory that only we, because of our biological roots, psychological understanding, and sociological awareness, can fully appreciate and apply. Bio is part of biopsychosocial and, therefore, it is not destroyed by a broader paradigm. Perhaps biopsychosocial fails because it is so easily divisible. Our trusty shibboleth is so easy to say. It takes only a few seconds, a quick breath, and then one moves toward one's own persuasion, bio, psycho, or social.

THE MIND-BODY CONTINUUM

A cornerstone of psychiatrists' adoption of a biopsychosocial framework lies in the resolution of the mind/brain dichotomy. In his Vestermark address of 1986, entitled "Are Psychiatric Educators 'Losing the Mind'?" (9), Reiser addresses this problem in terms of psychiatric education. He is particularly interested in the problem of a broad approach and the retention of mind in the training of psychiatrists. He says:

> With the expansion of our neurobiological data base and the movement to "remedicalize" psychiatry, some psychiatrists think that only a biologically based understanding of the brain should be retained in residency curricula and the "soft," nonbiological considerations of, and clinical approaches to, the mind and mental function should be dropped from psychiatry and relegated to allied disciplines. However, even though the brain is the organ that subserves the functions of the mind, brain and mind are not the same thing. Brain science does not yet, and probably never will, fully explain the mind or make mental functions fully understandable, especially in ways that can facilitate dealing with many of the important clinical problems encountered in medical as well as psychiatric practice—problems that can be understood as having arisen ultimately in response to inner experience and as reflecting the human condition. (9)

This is further supported by such creative explorations as those done by Jonathan Winson (10). Reiser says:

> Admittedly, data and theories that address common phenomena but come from different disciplinary domains are not easily or even partially—if at all—reconcilable. All the same, there is a vast and rapidly growing body of experimental data and theoretical developments in the field of cognitive psychology and neuropsychology that bears quite directly on psychoanalytic concepts and that should facilitate reconciliation of psychoanalytic concepts with neurobiology. There has been some promising efforts to develop such bridging concepts and principles . . . and students and residents should be made aware of them. (9)

In addressing the issue of medical education Reiser says, "the future physician will require knowledge of and proficiency in understanding and managing the doctor-patient relationship and applying psychosocial, psychological and psychopharmacological treatment modalities in conjunction with the conventional medical and surgical treatments" (9).

Reiser describes a teaching method in which he consults on cases, trying to approach them in the broadest manner, and introduces the mind as an aspect of understanding the total case. He says:

> During recent years, I have found myself more and more "at sea" after some of the presentations—having more and more difficulty getting a satisfactory image and idea of the patient and his or her life situation . . . .
>
> Then I caught on: in the presentations that left me at sea, the residents were not providing the kinds of information that I needed. I talked with some of the residents and found that their approach and mind set in the interviews were astoundingly unpsychological. Once they had done the *DSM-III* "inventory" and had identified target symptoms for pharmacotherapy, the diagnostic workup and meaningful communication stopped . . . . Clearly, this lack of curiosity and wish to *understand* must have adversely affected the patient and his or her ability to form a therapeutic relationship . . . .
>
> A fundamental change of this nature is bound to diminish the attractiveness of psychiatry to those medical students who are interested in the mind and to those students who are interested in talking with patients. Over time, fewer and fewer physician-psychiatrists and more and

> more nonmedical psychotherapists would be the ones to bring psychologically based skills and knowledge to bear in the care of patients, and fewer psychiatrists would have been prepared to educate medical students in these important matters. Following this course, as a profession we will have "lost the mind" by default. (9)

The biopsychosocial paradigm should be the hallmark by which all medical, psychiatric, educational, clinical, and research work is done. Although complex and much more difficult than biomedical research and biomedical clinical care, it is essential if medicine and psychiatry are to move into the twenty-first century, incorporating all elements of our technological, scientific, and humanistic explosions and providing a foundation for the relationship among mind, brain, body, and the world at large.

THE BIOPSYCHOSOCIAL PARADIGM AND EDUCATION

Two recent studies suggest that we are not educating "biopsychosocial thinkers" in our psychiatric training programs. In a recent study by Silverman et al. (11), Harvard students were asked to respond to patient interviews with questions for further information. Ninety percent of the students' requests for additional data to videotaped, simulated patient interviews were for biological information. "Approximately 66 percent of all respondents in six separate trials failed to request a single psychological or social item concerning the patient" (11). These investigators concluded that the integrated approach seems honored much more in theory than in practice. They seem to concur with the thesis of Engel's paper when they say:

> there is a clear need for the explicit presentation and study of the conceptual models that govern medical practice .... that the trends of dehumanization of medical practice and excessive use of diagnostic technologies, so widely decried in the media and often attributed to the need to practice "defensive" medicine, may actually have their roots in unaddressed areas of medical theory and philosophy (11).

These investigations found that, even at the medical student level, the biopsychosocial model is more of a shibboleth than a reality, a concept embraced by a few internists and many psychiatrists, all of whom play a small role when compared to the abundant number of teachers, mentors, and theorists who take the future generations of physicians down a biomedical path.

THE BIOPSYCHOSOCIAL PARADIGM AND CLINICAL PRACTICE

In another example, Vasile et al. (12) address a biopsychosocial approach to treating patients with affective disorders. In their paper, they corroborate what we already learned from Silverman et al., that we may be too far down the road in the biomedical model to ever go back to a broader view of the patient. A series of consultations were done at a clinic that had a large number of depressed patients. In a review of the consultations, the continuous missing link was the request for information pertaining to the psychotherapeutic aspects of care and treatment. The statistics speak for themselves. There were only three consultative inquiries concerning psychotherapy, yet the consultants remarked on psychotherapy 153 times. There were 160 requests for psychopharmacological information and the consultants spoke to that aspect of care 175 times. Certainly, the lack of interest by the treatment team in the psychotherapeutic aspects of patient care is frightening when one is attempting to look at biopsychosocial as a paradigm that should be used by all treaters. Apparently, we have gone so far down the biomedical pathway that psychotherapy, which used to be the only psychiatric intervention, is now rarely even considered.

Vasile et al. (12) make some remarks that go back to the discussion of Dr. Thad Barringer and the transformation of his clinical approach. They describe reaction and proaction models of clinical care. The reaction model emphasizes the patient as a passive recipient of a treatment technique, be it pharmacological or behavioral; the proaction model, by contrast, focuses on the patient as a collaborator in the therapeutic process responsible for and attempting to understand the conscious or unconscious factors that may be motivating dysfunctional behavior.

Clinical practice demands that the clinician have the ability to shift from one model to the other and to integrate both as required by the patient's needs. Although Vasile et al. and Barringer come at this from a different perspective than that put forward by Engel and other authors, the demand is the same; that flexibility, in terms of diagnostic and treatment paradigms, be paramount in the training and development, not only of psychiatrists, but of all physicians.

How could the clinical world be made more biopsychosocial? In psychiatry, it requires attention to all three spheres in the diagnosis, treatment plan, and management of all patients. The case I saw in rounds is only one example of applying the paradigm as widely as possible. A number of authors have begun to apply the biopsychosocial model to specific diagnostic categories, e.g., schizophrenia (Waltzer [13]), risk-taking behaviors in adolescents (Irwin and Millstein [14]), and acquired immune deficiency syndrome (AIDS) (Cohen and Weisman [15]). Others are writing about the paradigm as it applies to family practice (Schulberg et. al. [16]), the primary care physician (Lipsitt [17]), and the internists (Swisher [18]).

The Osheroff-Chestnut Lodge lawsuit represents a failure to think broadly about "biopsychosocial" ideas and to look instead for the limitations of each of the three spheres. In his recent speech on the Osheroff case in which he expresses his concern that the separation of psychotherapy from psychopharmacology is dangerous, Stone concludes:

> The future legal implications in the treatment of depressed patients depends not on Osheroff, but on the leaders of the American psychiatric profession, like those gathered here. If we take our differing professional perspectives into the courtroom, we can experience the intoxicating and self-righteous exercise of legal power, but the law is a blunt instrument and the legal blow we strike may be detrimental to our patients as well as to our profession, and to the further development of scientific psychiatry." (personal communication)

The argument between Stone and Klerman about the Osheroff case is one in which the plea for the acceptance of diversity in the biopsychosocial sphere is raised to the highest level of conflict. Reiser comments as follows:

> Authoritative stature and accomplishment properly carry with them enthusiasm and "conviction" regarding the special place and value of one's chosen field, but for a faculty to be pluralistic in the particular sense I wish to convey, individual experts should also be open-minded, respectful, and receptive to contributions of other faculty members who are also experts. These faculty members are just as committed to other areas and approaches that address phenomena of common interests, and their contributions are supplementary and complementary rather than antithetical. (9)

In medicine, doctors must recognize the effects of their anachronistic, reductionistic approach to patients. The patient's fears; the patient's lifestyle; the stress on the patient from intrapsychic, interpersonal, and environmental stimuli; the doctor's fears; the doctor's personal life and demands; and the stress on the doctor from intrapsychic, interpersonal, and environmental stimuli must all be recognized as legitimate avenues of inquiry and important etiologic and aggravating elements in all diseases.

In many of his papers, Engel includes cases demonstrating that his medical approach is equally shared and tempered by his thinking about the psychosocial issues which create the events in the hospital and the office. He, like us, relies heavily on symbols, words, phrases, metaphors, aspects of language and communication that not only remain largely untaught in medical schools and graduate training programs but are disdained as meaningless, useless, and "unscientific."

Many argue that it is difficult to concentrate on doctor/patient relationships and biopsychosocial issues in the current economic climate. A recent editorial by Winkenberder and Ball (19) speaks eloquently to this problem. They say that the physician/patient relationship, once based on a covenant whereby the patient trusted the physician to do what was best for him or her, is being transformed into a contractual relationship in which the physician provides a specified measurable service at a negotiated price. It is hard for us in psychiatry to think about the paradigm by which we care optimally for patients in a climate that speaks vigorously against the doctor/patient relationship. These authors call out for a reevaluation of the values and priorities of the system and for an economic restructuring that would support putting the patient first. The biopsychosocial shibboleth must become a reality in which first consideration is given to the patient, rather than to the demands of insurance companies or the ideologies of any given group of psychiatrists or physicians approaching patients from a reductionistic, that is, solely from a bio, psycho, or social, point of view.

THE BIOPSYCHOSOCIAL PARADIGM AND RESEARCH

Finally, the application of the biopsychosocial paradigm to research is the most vital and perhaps the most difficult of all challenges. How can a cell biologist or an investigator in the areas of imaging or brain function include psychological or sociocultural considerations in his or her research design? That begs the question, Are researchers knowledgeable about the other research variables? Can they think in broader, wider paradigms so that their small issue does not overshadow for them the bigger picture? The question that Klerman raises about efficacy of psychotherapy is an important one. However, by insisting on full disclosure of the doctor's basic thinking about his or her approach to therapy, he forces narrow rather than broad thinking and defensive medicine in lieu of creative biopsychosocial thinking. Rather, his question should put pressure on all researchers and it should, particularly, force those doing psychotherapy research to place their concepts in a larger frame and begin to develop and train a new generation of researchers who will focus on their narrow investigation, not with prejudice and disdain for those working in other vineyards, but rather with respect, understanding, and collaboration when possible so that the educator and clinicians will have a broad base of knowledge from which to ply their trades.

In his book, *Brain and Psyche* (10), Winson attempts to apply recent brain research and information about the functioning of the hypothalamus to the theory of dream interpretation, starting with Freud and revising it as a result of what we have learned recently about memory, retention, and recall. Coming at the process from a different angle, Winson is attempting to take the psychological piece of biopsychosocial and plant it firmly in the biological sphere as a necessary part of an integrated approach. All of these separate parts must come together in a philosophy that goes well beyond any single aspect of the grouping. Winson, although neither a psychiatrist nor a physician, demonstrates that one must be thoroughly grounded in every aspect and must be knowledgeable, in his case, of both the psychology of dreams and dream interpretation, as well as the biology of the brain.

Engel, with extraordinary flexibility and willingness to examine and reexamine the thesis upon which he has built his creative approach to patient care and

medicine, gives us a hint of his moving ahead and perhaps away from biopsychosocial when he says, "and finally, the resolution of the gap between psychiatry and the rest of medicine and that between clinical medicine and science awaits adoption of a more inclusive paradigm, one no longer disallowing a scientific approach to the phenomenal world in human affairs" (in preparation).

CONCLUSIONS

My concern about how psychiatry is perceived in the public mind, in the media and in the medical community, remains great. Every policy decision of our organization is viewed from this perspective. Will subspecialization add to our struggle and fragment us? Will struggles with our nonphysician colleagues hurt our image and our ability to practice from a biopsychosocial paradigm? Will compromise and expediency in the economic sphere require us to sacrifice ethics, our Hippocratic ideals, and a broader biopsychosocial approach to our own clinical work?

Throughout this paper I have woven the concept of the human aspect of medical care, the psychosocial as the human element in disease and health, because it is the missing element of many medical and psychiatric encounters; it is the missing element in much biomedical and psychiatric research; and it is the missing element in the application of biomedical science and biological diseases in our approach to families and patients. Dehumanization is the dangerous risk we run in our constant effort to read the tea leaves and try to come down on the "right" side rather than taking the more difficult, uncertain road in which we combine humaneness and biological aspects into a single care system that exalts the patient and puts the patient first.

My theme for the Presidential Year is "Overcoming Stigma." This paper is intimately related to the theme by stressing how we might best overcome it. I maintain that psychiatric stigma is best handled not by battering our heads against stone walls, not by insisting that people stop hating us, fearing us, deriding us, undercutting us, and competing with us, but rather by establishing that we are at the forefront of the modern medical paradigm. The biopsychosocial concept ought not be a password leading to more restrictive, conservative, unidimensional approaches. We have to be willing to accept the uncertainty of how the other two elements fit (those which are not the primary ones to each of us) into the one that many of us have as our major and singular direction for our work. In many ways, we are a unique specialty of medicine and a unique profession. We represent a potential for combining the scientific in the orthodox biomedical sense and the humane in the psychosocial sense. The challenge is to move 35,000 members of this organization toward a broader view and a greater openness, to the valid and meaningful approaches of Engel, Foss and Rothenberg, McHugh and Slavney (20, 21), and others. Such a move would allow us to be united, forward looking, and creative in our development. We know we have the capacity to be limited, unidimensional, focused on a single aspect, divisive, sliding backward, unable to continue our profession's development. Our growth and strength depend upon all of you, the members of the APA, who must begin to approach every aspect of psychiatry from a biopsychosocial point of view, to recognize the paradigm, not as the shibboleth that I have described, but as a real and extraordinary opportunity to take modern science and health and the science of health and illness meaningfully and exaltedly into the twenty-first century.

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George H. Pollock, M.D., Ph.D., One Hundred Sixteenth President, 1987–1988

Melvin Sabshin, M.D.

Twenty-five years ago George Pollock described Franz Alexander as "the interminably youthful man" who "was always searching for new horizons, new ideas, never satisfied to stop" (1, p. 229). I cannot find a better way to describe our current President than his own appraisal of Alexander. What does one say about a man whose curriculum vitae lists more than 200 publications and also includes current membership in 89 associations and societies—ranging from the American Academy of Child and Adolescent Psychiatry to the American Association for Geriatric Society, and from the American Ethnological Society to the American Institute of Biological Sciences? How does one understand an international leader in psychiatry and psychoanalysis whose range of interest in science is matched by his interest in the arts? He has worked for and identified with Warren McCulloch as well as Alexander; he has written about Bach and Mahler as well as Van Gogh.

These days in psychiatry it is not so fashionable to paint our field in such broad brush strokes. The somewhat limiting winds of logical positivism, empiricism, and objectification predominate. Reductionism—especially biological reductionism—becomes the ideal mode for elite academic career advancement; to be interested in the philosophy of science too early in one's career shows a dangerous propensity of becoming a deviationist. Similarly, an interest in psychoanalysis does not bode well for such an academic careerist. Ironically, this parallels a tendency still present in psychoanalysis to view broad interests in neurosciences or even general psychiatry with some alarm when considering the credentials of a psychoanalyst.

George Pollock rises above these fashions, modes, and trends. While he has been deeply involved with his psychoanalytic leadership roles—indeed, he has been President of the Chicago Institute for Psychoanalysis for 18 years and is past-president of the American Psychoanalytic Association—his enormous energy and his intellectual curiosity have continued a search for *still another bridge*—beyond the immediate horizon.

Last year, in a celebration for George's assumption of the president-elect's position in APA, a number of his friends and colleagues and his family wrote brief appreciations of him. I was particularly touched by the collective statement of his five children. The following is a paraphrase of part of what they said:

> Papa, you are a man of many skills; not only are we intensely proud of you for your professional achievements but also we fondly admire your ability to change tires on the Pennsylvania Turnpike, to keep us well supplied with books from bookstores all over the Continental USA and beyond—Your love and interest are a continuing source of strength for us. We learn from your wisdom, your boundless energy and your advice.

All of George and Beverly's children have done well by nonconventional as well as conventional standards, which says a good deal about their parents as well as themselves. For me, the fact that three of them are physicians is lagniappe—marvelous icing on the cake.

George Pollock has also been a good parent in many of his APA leadership roles. As treasurer he was prudent and wise—during occasional difficult periods. While chair of the Joint Reference Committee during his year as president-elect, he wanted each flower to bloom—even to the point of encouraging the ordinarily nonvoting component chairs to have a vote, albeit informal, in the deliberations. Similarly, during his presidency he facilitated wide-ranging discussion and balanced decision making; while process concerns often seemed more dominant than content, George Pollock had firm opinions and clearly preferred negotiations with the field's adversaries; he also reinforced the primacy of the clinician's interests and the survival of the solo private practitioner of psychotherapy.

George Pollock received his M.D. and Ph.D. degrees from the University of Illinois. His personal research interests have spanned a variety of fields with very heavy concentration earlier on neurophysiology and psychosomatic processes. He carried Alexander's specificity formulations to their logical apogee. In recent years, work on psychosocial processes has predominated. These included interest in the life cycle as well as studies of loss, bereavement, and preventive intervention. Not surprisingly, George Pollock has also been interested in creativity. It oozes from every pore. Taken all together, these interests and skills mark an extraordinary man. Occasionally he swims up-

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stream—and occasionally his intense efforts to find support for a less faddish style of scholarship have had problems. More importantly, however, we at APA have been lucky to have him as a leader at this time in our history. He has been a good friend to me, an excellent teacher, and a symbol, I hope, for a renaissance for psychiatry when *we* all cross still another bridge not yet clearly in sight.

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Conceptual and Methodological Issues in Comparative Studies of Psychotherapy and Pharmacotherapy, II: Nature and Timing of Treatment Effects

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This is the second of two articles on the conceptual and methodological problems involved in comparing the effectiveness of drugs and psychotherapy in the treatment of mental disorders. Part II focuses on differences between psychotherapy and pharmacotherapy in the nature of treatment effects and related goals for treatment, differences in the time course of treatment effects, and potential sources of bias in the research setting. In designing comparative studies of psychotherapy and pharmacotherapy, investigators should address methodological choices explicitly and consider the implications for interpretation of findings.

(Am J Psychiatry 1988; 145:1070–1076)

Studies that compare pharmacotherapy and psychotherapy must confront a number of conceptual and methodological problems because of the intrinsic differences between these two forms of treatment. The first article in this series, which appeared in the August issue of the *Journal*, focused on differences in active ingredients and purported mechanisms of change. In this paper we address differences in the nature of the expected treatment effects and treatment goals and differences in the time course of treatment effects. We also consider potential sources of bias in the research setting.

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NATURE OF TREATMENT EFFECTS

Closely related to the different mechanisms of change in psychotherapy and pharmacotherapy are differences in the nature of the expected treatment effects. The expectation of different effects raises two major issues for the design and methodology of a comparative study: 1) the appropriateness of the patient sample for each of the treatments and 2) the adequacy of the outcome evaluation in assessing the specific effects of each of the treatments.

A more general issue that is highlighted by the focus on the differential effects of these two forms of treatment should also be mentioned. A comparative study of psychotherapy and pharmacotherapy may be conceived of as a "horse race" to determine which of the treatments is more effective or, alternatively, as an attempt to address more differentiated, and ultimately more meaningful, questions regarding which patients may be helped more by each of these approaches and in what ways. The latter formulation seems a more productive route to the eventual clinical goal of determining the most beneficial treatment for individual patients.

Appropriate Patient Sample

A comparative outcome study must ensure, first, that each of the treatments being investigated is relevant to the patient sample being treated and, second, must guard against biases in patient selection that can influence the results in favor of one or another treatment. These requirements have implications for both inclusion and exclusion criteria.

Inclusion criteria. The advent of structured diagnostic interviews and decision rules (e.g., the Feighner cri-

teria, the Schedule for Affective Disorders and Schizophrenia and its companion Research Diagnostic Criteria [RDC], the Diagnostic Interview Schedule, and *DSM-III*) has enhanced the reliability of psychiatric diagnosis, and most clinical research now targets specific diagnostic groups for inclusion in research protocols. Despite these efforts, considerable heterogeneity may still exist within samples selected for investigation; for instance, there may be differences in subtypes of a disorder, symptom patterns, or presence of concurrent disorders. This heterogeneity becomes critical in comparing the effects of drugs and psychotherapy if it is assumed that mechanisms of action are operating which have different implications for different subpopulations (e.g., patients with vegetative symptoms versus difficulties in social functioning).

In comparative treatment studies of depressed patients, for example, it is important to include the subtypes of depression considered especially responsive to each type of treatment. A prime example is the need to include patients with endogenous depression, for whom drugs are expected to be particularly effective. At the same time, a study involving patients with only endogenous depression might not constitute a fair test for psychotherapy if one is considering the relative effectiveness of the treatments for depressed outpatients in general. One could, however, rephrase the research question to take this into account, e.g., "What is the relative effectiveness of pharmacotherapy and psychotherapy in outpatients with endogenous depression?" and limit one's interpretation of the results accordingly.

Where sufficient information is available, it would be ideal, of course, to include relevant subgroups as factors in a research design. In the more frequent circumstance, in which predictor analyses are conducted, it is important to include variables presumed to be influential in the outcome of each form of treatment (e.g., acuteness of onset, level of social functioning). Of special significance are those variables specifically expected to differentiate drug and psychotherapy conditions. The report that a measure of self-control skills differentially predicted drug and psychotherapy responders (1) is encouraging in this regard. Similarly, Prusoff et al. (2) reported that the RDC diagnosis of endogenous depression was a significant predictor of differential response to drug, psychotherapy, and a drug-psychotherapy combination.

Exclusion criteria. The difference in the natures of psychotherapy and pharmacotherapy has implications not only for which patients should be included in a comparative study but also for which patients may have to be excluded. Most obvious here is the necessity to exclude patients for whom the use of a particular drug is contraindicated, e.g., patients who are currently receiving medications that could interact negatively with the investigational drug or who have medical illnesses which preclude use of the study medication. Those exclusions could result in a physically healthier patient sample in a comparative study than is usually the case for studies including only psychotherapy conditions.

The appropriateness of specific forms of psychotherapy could also be limited because of certain patient characteristics. For example, patients who are unable or unwilling to reflect on their own mental processes may not be suitable candidates for a psychodynamic form of psychotherapy. Further, proponents of brief dynamically oriented therapy have developed guidelines for patient selection that tend to be more stringent than the usual clinical standards (3–5), and adherence to such selection criteria would limit the sample for a comparative study and the ability to generalize from the results. Actively suicidal patients tend to be excluded from studies that include a psychotherapy condition because of the need to provide symptom relief as rapidly as possible. Such exclusions may be questionable, however, since the only available research data (6) suggest that specific forms of psychotherapy may, in fact, reduce suicidal ideation as rapidly as drug treatment.

In order to limit a sample to patients most likely to benefit from a particular treatment approach, some investigators exclude those patients who have failed to respond to a previous trial of that treatment (7). If nonresponders to only one of the treatments being compared are excluded, however, biases are clearly introduced in favor of that treatment. Since only drug nonresponders were excluded in the Rush et al. study comparing cognitive therapy and imipramine (8), it is indeed fortunate that the cognitive therapy condition was more effective, for the reverse findings would have been difficult to interpret. Weissman et al. (9) discussed differences in outcome and sequencing of effects in maintenance treatment of depressed patients with psychotherapy versus drugs, but, since their sample consisted entirely of patients who had responded favorably to medication during an acute episode, their findings are limited to initially drug-responsive patients.

In summary, limiting a study sample to patients appropriate for either the pharmacotherapy or psychotherapy condition may have serious implications for comparative outcome findings. We would especially like to stress the importance of recognizing the nature of the final patient sample when interpreting and generalizing from the results of a study.

Evaluation of Outcome

The differences in posited active ingredients and mechanisms of change lead also to different goals for psychotherapy and pharmacotherapy and to differences in related measures of change. Psychotropic drug treatment is, like most medical treatments, directed at a specific symptom-defined syndrome and is focused on the alleviation of targeted symptoms and the remission of the episode of illness. Psychotherapeutic approaches, on the other hand, are often directed at major areas of the patient's intrapsychic and interpersonal

functioning. As summarized many years ago by Parloff et al. (10), three general goals of many forms of psychotherapy are comfort, social effectiveness, and self-awareness. Although the advent of the behavior therapies has resulted in an increased focus on the reduction of specific behavioral symptoms, psychodynamically and humanistically oriented therapies continue to focus on broader areas of functioning and subjective experience.

In order to be fair to each treatment, it is necessary to assess the changes that each approach attempts to achieve. In a study of the treatment of depression one must include not only measures of depressive symptoms (considered important within all approaches) but also measures of expected changes specific to each approach. Thus, it is important to include measures of interpersonal functioning and patient attitudes and self-concepts, considered central by psychotherapy theorists (6, 11–13), and measures of vegetative symptoms, suicidal ideation, and, perhaps, physiologic function, which are emphasized by pharmacological theorists. Patients in all treatment conditions should, of course, be assessed on all measures so that it will be possible to examine unexpected as well as predicted effects and to study thoroughly the differential effectiveness of the different treatment forms. Since an ideal outcome battery for a comparative study would be very extensive, the researcher is faced with an assessment dilemma that is common but even more salient in comparative research: How does one balance the comprehensiveness of the battery against the possibility of overburdening the patient and other participants in the study? This latter possibility creates legitimate concerns that may result in some reductions in size of the "ideal" battery. However, it is essential that the researcher attempt to capture at least some of the posited specific effects of each of the treatment approaches being compared.

One further problem that arises because of the different emphases of various treatments concerns assessments made by therapists. The nature of a particular treatment supplies a therapist with a different experience of the patient. The different information available in pharmacotherapy and psychotherapy conditions could lead to systematically different therapist ratings of the same phenomenon. For example, a psychotherapist's more extensive discussion of a patient's affective experience in a variety of life areas could lead to ratings of depressed mood that differ from the patient's direct response to a simple inquiry about depressed mood. In addition, a therapist may not be able to make assessments that are specifically relevant to another treatment without departing from his or her own treatment approach. In the pilot phase of the NIMH Treatment of Depression Collaborative Research Program, for instance, we found that psychotherapists could not always complete all of the items on the Hamilton Rating Scale for Depression, a psychiatric scale heavily weighted with somatic symptoms, while pharmacotherapists were sometimes not able to provide all of the answers to the General Life Functioning Scale, which included items such as "How close was the patient able to feel to at least one other person?" In the NIMH collaborative study a decision was made to maintain the integrity of each treatment, i.e., not to have the therapist depart from his or her prescribed approach in order to complete a particular instrument. As a result of this decision we had to deal with the statistical problems related to missing data, but this seemed less of a hazard than changing the nature of the treatments themselves to get complete data.

Since therapists in different treatment conditions may have not only different goals for treatment but also different criteria for the attainment of these goals, differential outcome findings based on the therapist's perspective may reflect the therapist's standards as well as the patient's actual functioning. The possibility of such a phenomenon is suggested by the results of a study by Sloane et al. (14), in which ratings by psychodynamically oriented therapists of improvement in patients' sexual adjustment were lower than the patients' own ratings, whereas the reverse was true for behavior therapists. Differences between psychotherapists and pharmacotherapists in their criteria for change may well exist and should be considered in interpreting findings based on therapist assessments. In addition, of course, it is important to include in any comparative study assessments by evaluators who are independent of the treatment process. (This point is discussed further in the section Sources of Bias in the Research Setting.)

TIME COURSE OF TREATMENT EFFECTS

The different mechanisms of action for pharmacotherapy and psychotherapy are reflected not only in the nature of the treatment effects but also in their timing. In general, psychotropic drugs are expected to work more rapidly, while psychotherapy, although it may have an immediate effect on the patient's hope for improvement, is generally expected to bring about change more slowly and cumulatively. The temporal order of various kinds of effects (e.g., somatic versus cognitive) may also differ. Further, some of the effects of psychotherapy may be expected to manifest themselves more clearly in the period after treatment, while this is not the case for drugs. These differences in temporal course have implications for the design of a comparative study in terms of the total duration of treatment (discussed in part I of our series) and the timing of evaluations of patient status and improvement. Differences in therapists' (and patients') expectations regarding the time at which treatment effects should appear may also have an impact on comparative study results through their influence on such factors as therapist morale and patient attrition.

Timing of Evaluations

Evaluations may be held during the course of treatment for a variety of purposes: to assess whether there are differences in the rapidity of response to different treatments (which may be especially important in regard to life-threatening symptoms, such as severe suicidal ideation), to explore the actual length of treatment necessary to bring about significant change, to simply track and attempt to understand the temporal course of symptom reduction for different treatments, and to test theoretical predictions about the differential course of symptom change for different forms of treatment. The use and timing of interim evaluations must thus be based on the questions being asked in a particular study, as well as whatever knowledge is available about the temporal course of the treatments. For example, if a major hypothesis is that the drug treatment but not the psychotherapy will effect significant improvement in 4 weeks, one interim evaluation might be held at that time. For the exploration of sequencing of effects throughout the course of treatment, however, it may be necessary to conduct evaluations on a weekly or biweekly basis. And, once again, a balance must be sought between the practical and theoretical aims of the research project and the need not to overburden the patient (and research staff).

In studies of depressed outpatients, researchers have used interim evaluations both to explore the differential course of symptom reduction and to test specific theoretical predictions. DiMascio et al. (6) reported that, despite a lack of differences in overall symptom reduction, amitriptyline treatment and interpersonal therapy produced different temporal courses; amitriptyline had major effects, often within the first week of treatment, on vegetative symptoms, and interpersonal therapy had somewhat later effects, primarily on such symptoms as mood, suicidal ideation, work, and interests. The temporal course of reductions in specific symptoms has also been examined to test predictions from cognitive theory (15).

In a comparative study of pharmacotherapy and psychotherapy, the need to remove the patient gradually from medication results in a problem regarding the timing of termination evaluations. Should termination evaluations be held before or after this tapering off period? In the well-known study of cognitive therapy and imipramine reported by Rush et al. (8), medication was tapered off during the last 2 weeks of the 12-week treatment and before the termination evaluation. These researchers recommended that future studies not taper the medication until after the conclusion of the treatment period so that termination evaluations would not be affected by the reduction in drug dose, which might create a bias against the drug condition. This recommendation was heeded in both the NIMH program and in the Murphy et al. (16) replication of the Rush et al. study. It should be pointed out, however, that this alternative raises other problems in interpretation. If the patient is still receiving a fairly high dose of the drug, one may not be getting a clear picture of the treatment effects at "termination." This dilemma is not easily resolved, but it may be advisable to carry out evaluations both before and after tapering off.

This brings us to the issue of follow-up evaluations. There has been an increasing awareness of the need for follow-up evaluations in treatment research, especially when studying disorders characterized by fairly high rates of both relapse and recurrence, such as depression. Follow-up evaluations may also, however, reveal delayed effects of treatment, and these may be more pronounced for psychotherapy than for drug treatment. Kubie, for example, maintained that "for some patients (psycho)therapy as a process of continuing psychological change and maturation may start only after all formal therapy has been terminated" (17, p. 882). Weissman et al. (13) provided one piece of research evidence supporting this position. They reported positive effects from psychotherapy (as compared to drugs) on social functioning at 1-year follow-up; these effects were not apparent at termination. It is always difficult to interpret findings from follow-up evaluations because of the role that may be played by additional treatment and other intervening events, and this is especially true for short-term interventions and extended follow-up periods. It is, nevertheless, important to explore long-term and possibly differential effects of treatment, with the recognition that one is embarking on a naturalistic, rather than an experimentally controlled, study.

Expectations Regarding Time Course

Effects on therapist and patient morale. Therapists' expectations regarding the timing of treatment effects may influence both the course and outcome of therapy, and this factor may differentially affect psychotherapy and drug treatments. A pharmacotherapist treating a patient with antidepressant drugs generally expects to see signs of the drug's effects, both therapeutic response and side effects, within the first few weeks of treatment. A psychotherapist, on the other hand, hopes to see some engagement in the therapeutic process by the patient during early weeks but generally does not expect marked improvement in a patient's functioning until some time later in treatment. If the pharmacotherapist does not observe an early treatment response, he or she may become demoralized and feel frustrated by the requirement to keep the patient in the research protocol, particularly if he or she is not allowed to switch to another drug. This response may be magnified when a placebo condition is included in the trial and the therapist might infer that the patient is not receiving an active drug. Demoralization of the pharmacotherapist may, of course, affect his or her behavior in ways that are detrimental to the outcome of the treatment. This situation creates a dilemma for the researcher, and several options may be considered: shortening the treatment period, allowing the therapist to switch to another specified drug, using a "doctor's choice" condition, or focusing specifically on therapist morale problems.

Differences in the expected course of symptom relief may affect the patients' expectations and morale as well as those of therapists. For example, if patients are accustomed to taking drugs, they may expect early remission of their symptoms. It is important, in this regard, to orient patients carefully, indicating the general expected time course for symptom relief but also stressing the variability in that time course for different patients. This problem may be more marked if a placebo condition is included in a study design, since patients are more likely to become discouraged if they conclude that they are receiving an inactive drug. The clinical management component of a pharmacotherapy condition may be crucial here, since it can provide for support and encouragement of patients.

Differential attrition. Different expectations about timing of treatment effects may be one source of differential attrition in a comparison of pharmacotherapy and psychotherapy and may affect the nature of the final sample of patients who complete treatment. For example, disappointment of patients (and therapists) when early symptom relief does not occur in a pharmacotherapy condition, coupled with the occasional occurrence of serious side effects early in treatment, may lead to a relatively high attrition rate. On the other hand, patients in a psychotherapy condition may be more likely to remain in a study even when they are not benefiting from treatment because of expectations that psychotherapy takes longer.

Although it would be ideal, from the perspective of data analysis and interpretation, if attrition were comparable in different treatment conditions, it is also important to remember that attrition may itself be one indicator of outcome, to the extent that it reflects the appropriateness and acceptability of a particular treatment for a particular patient population.

Differential attrition has many implications for data analysis and interpretation of findings. Both Lasky (18) and Hollon and Beck (7) have discussed some of the statistical and interpretive problems that result from differential attrition, and these will not be discussed at length here. We do want, however, to point out the importance of keeping careful records of the reasons for early termination, since these can help in understanding any differential attrition findings. Also, since attrition in the different conditions may involve different types of patients, demographic and clinical data should be analyzed to determine whether there are differences between treatments in both the patients lost to the study and those who complete the study. Finally, early termination evaluations should be held whenever possible; these can be used in end-point analyses that take into account the termination status of all patients.

SOURCES OF BIAS IN THE RESEARCH SETTING

Up to this point we have discussed some of the problems inherent in comparing such different treatments as psychotherapy and psychopharmacotherapy, and our major concern has been the fair comparison of the treatments and the clear interpretation of findings. Comparisons may also be biased toward one or another treatment because of factors in the setting in which the research is conducted. It is common knowledge that many comparative outcome studies have been conducted within a context in which one therapy is favored. Weissman's observation that in studies comparing different psychotherapies for depression "there has been a tendency for the treatment that is the usual modality of the research group to be shown as more efficacious by that group" (19, p. 1267) may hold for comparisons of psychotherapy and pharmacotherapy as well. Generally, the researcher will give more careful consideration to the definition and the implementation of the treatment condition with which he or she is more familiar and less attention to the competing treatment forms.

It is not only the primary investigator's orientation that may influence the comparative findings. Clinical research takes place in an institutional setting, and in such settings contacts with staff members other than the therapist can take on a special importance. All research staff members have their own expectations regarding the effectiveness of different treatments and their own preferences; these may, sometimes in very subtle ways, affect the outcome of a study. The areas in which research staff expectations and biases may influence a study include decisions regarding patient eligibility and assignment to specific treatments, assessments of change, additional staff support given during the course of the treatment trial, decisions regarding withdrawal of patients from the protocol, and referrals made at termination of treatment. Rather than discussing at length the various ways in which research staff attitudes and biases could exert an influence at each of these points in the study, we will simply make some recommendations for minimizing such influences.

First, it is important that random assignment to treatment conditions not occur until after informed consent has been obtained, the initial evaluation has been completed, and a decision has been made about the patient's eligibility for the study. It is crucial, of course, that the mechanism for random assignment be completely independent of the process of determining eligibility for the study.

Second, in addition to assessments of change by the patient and therapist, evaluations should also be made by a clinician independent of the treatment process and blind to a patient's treatment assignment. Blind evaluations are, in the real world, difficult to achieve (especially where the different treatments are carried out by different therapists), and this effort requires considerable cooperation by evaluators, patients, therapists, and other staff. The problem of "blind breaking" may be partially alleviated by careful initial instructions to patients, reminders before each evaluation not to identify the patient's therapist or treatment, and modifying the physical setting so that treatment rooms are separated from evaluation rooms.

It is important to instruct clinical evaluators to

maintain consistency in their interviewing procedures (regardless of guesses they may have about a patient's treatment assignment) and to monitor their performance. The attitudes of the clinical evaluators toward the different treatment approaches, as well as their actual guesses about each patient's assignment, should also be assessed.

Another consideration is additional staff support. Although it would be virtually impossible (and probably not desirable) to eliminate the effects of supportive interactions between patients and clinical evaluators and other staff members, it is important that research staff personnel resist efforts by the patient to draw them into an actively therapeutic relationship and that they redirect issues relevant to therapy back to the treatment room. It is particularly important to try to eliminate differential treatment by research staff of patients in different treatment conditions. Critical here is the need for all staff members to have well-defined roles and to be instructed that they should be consistent in their roles with all patients regardless of known or suspected treatment assignment. Staff members should be monitored during the study to ensure adherence to roles.

It is also crucial that withdrawal criteria be developed and applied uniformly across all treatment conditions. Although care should be taken to maintain as much consistency as possible, it is important to recognize that some reasons for withdrawing a patient may be particular to a specific treatment (e.g., serious side effects in a pharmacotherapy condition or a severe sleep disturbance in psychotherapy). Such results could provide an important index to the applicability of treatments for different patients or for different complaints.

As much consistency as possible is also desirable in making referrals for additional treatment at termination, especially if follow-up data are to be collected. General consistency in referral decisions can be maintained if the major criterion for referral is the patient's clinical condition at termination. There may, again, be some legitimate differences in referral decisions due to factors intrinsic to each of the treatment conditions, e.g., referral for psychotherapy of a patient whose deteriorating marital situation could not be adequately dealt with in pharmacotherapy or referral for pharmacotherapy of a patient with a deteriorating symptom course unresponsive to a psychotherapy. These outcome-based decisions may again indicate the limits of applicability of particular treatments.

COMMENT

Many of the issues discussed in this two-part series involve dilemmas that must be faced and decisions that must be made in designing and implementing comparative studies of psychotherapy and pharmacotherapy. In making these decisions, one must often weigh the importance of maintaining scientific rigor, on the one hand, and maintaining the clinical relevance and integrity of the treatment conditions, on the other. Methodological discussions often lean in the direction of scientific rigor, stressing the importance of keeping variables constant across conditions. The present discussion, to the extent that it has a bias, probably leans in the direction of maintaining the integrity and distinctiveness of each treatment condition. It is important to recognize, however, that there are no "correct answers" in this area and that choices may differ depending on the nature of the treatments and the purpose of the particular study. To the extent that one is concerned with the efficacy of the treatment as practiced, one would probably lean toward maintaining the integrity of each treatment package; to the extent that one wants to isolate the effects of specific ingredients or components of the treatments, one might lean toward maintaining the consistency of all other factors.

We recognize that the list of issues we have raised may seem formidable to investigators, especially those who are new to this area of research. In fact, however, either explicitly or implicitly, any comparative treatment study will have to address most or all of these issues. Our purpose is to encourage researchers to be explicit in their consideration and communication of the decisions that they make and their consequences.

Many of the questions that have been raised reflect choices that must be made in any study of treatment outcome. We have considered the impact that particular decisions may have on the adequate and equitable comparison of psychotherapy and pharmacotherapy and have pointed out some of the implications of these decisions for the interpretation of findings and the ability to generalize from them.

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A Multidimensional Approach to the Genetics of Schizophrenia

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To determine which dimensions of psychopathology are associated with a greater liability to develop schizophrenia, the authors examined the case histories of 151 monozygotic probands from five twin studies. Proband twins from pairs concordant for schizophrenia had greater numbers of negative symptoms, poorer premorbid adjustment, fewer paranoid symptoms, and earlier ages at onset than probands from discordant pairs. In discriminant analyses, negative symptoms, premorbid social competence, and paranoid symptoms each contributed to the discrimination between concordant and discordant pairs. These results provide support for Strauss et al.'s suggestion that these three types of symptoms reflect three different functional processes in the development of schizophrenia.

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In 1974, Strauss et al. proposed that three different processes underlie the diverse symptoms and signs of schizophrenia (1). Three kinds of symptoms—positive symptoms, negative symptoms, and disorders in relating—were thought to reflect these processes, and it was suggested that each process might have a different etiology and response to treatment. Although a great deal of previous research on schizophrenia had examined premorbid social adjustment (2), in drawing attention to the distinction between positive and negative symptoms, Strauss et al. anticipated what has now become a major area of interest in recent research on schizophrenia (3–8).

Current theoretical and empirical analyses of the distinction between positive and negative symptoms, however, have not been consistent in describing the role of the third type of symptom discussed by Strauss and his colleagues. In some approaches, social withdrawal is considered a negative symptom (5), whereas in other approaches it is not considered to be related to the distinction between positive and negative symptoms (4). There is evidence that premorbid social adjustment and negative symptoms are associated (6, 7, 9–11), which suggests that poor premorbid social adjustment may be an antecedent of negative symptoms in schizophrenia. But on the basis of the data that are currently available, it is not possible to determine whether disorders in social relationships are part of a longitudinal process that precedes negative symptoms, are one type of negative symptom, or reflect a separate process in the development of schizophrenia.

There are also other dimensions that have played a prominent role in research on schizophrenia which have not been considered in recent approaches to the distinction between positive and negative symptoms. Among these are severity, which has often been assessed by means of the acute-chronic (12) or process-reactive (13) distinctions, and paranoid symptoms, usually examined by means of a distinction between paranoid and nonparanoid subtypes of schizophrenia (14). It may be that these two dimensions, severity and paranoid symptoms, also reflect basic functional processes that underlie the diverse manifestations of schizophrenia.

In previous research, we examined the relationships

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between positive and negative symptoms and concordance in the case histories of 151 monozygotic twin pairs in which at least one member of each pair (the proband) had received a diagnosis of schizophrenia (15). Concordance rates for schizophrenia were higher when proband twins had a greater number of negative symptoms; probands from concordant twin pairs also had significantly greater numbers of negative symptoms than probands from discordant twin pairs. Such relationships with concordance have been interpreted as providing evidence of genetic influences (16). But it is also possible that they reflect the contribution of nongenetic familial factors which may be associated with the higher liability to illness characterizing proband twins from concordant pairs (17).

To determine whether other variables that may reflect important processes in the development of schizophrenia are also associated with concordance, we have now examined premorbid adjustment, severity, and paranoid symptoms in these twin pairs. Because of interrelationships among these variables, discriminant analyses were conducted in order to identify the unique contributions of these variables to discriminating concordant from discordant twin pair probands. A preliminary report of univariate analyses of the relationships between concordance and premorbid adjustment and severity has appeared in a review of the literature on genetics and the phenomenology of schizophrenia (18).

METHOD

The case histories of all monozygotic schizophrenic probands and their co-twins from the five twin studies of schizophrenia that have case histories published in English (19–26) were assembled. These 302 case histories of 151 monozygotic twin pairs were carefully edited to remove all identifying information that might enable a rater to match a proband with his or her co-twin. Zygosity and family history data were also deleted from the case histories before they were rated. We have limited the analyses to monozygotic twins because their greater degree of concordance allows a clearer examination of the relationships between genetic influences and other variables. In addition, for several of these twin studies, dizygotic twin case histories have not been published.

In 139 of these 151 monozygotic twin pairs, a single twin was identified by the ascertainment method used in the twin study from which the pair was drawn; these twins, who were clearly identified as such in the case histories, have been considered probands in all of the following analyses. In 12 of the twin pairs, both twins were independently ascertained and would be considered probands in the calculation of probandwise concordance rates. Probandwise concordance rates reflect co-twins' risk of schizophrenia and are therefore comparable to the morbidity risks of schizophrenia for other groups of relatives and the general population (19, 27); our hypotheses and analyses, however, are not intended to address such epidemiological questions regarding risk of schizophrenia in monozygotic co-twins. For this reason, and because tests of statistical significance are more directly applicable to pairwise analyses (28, 29), we have designated the *initially* ascertained proband twin in each of the 12 doubly ascertained pairs as the proband in all of the following analyses. (For four doubly ascertained pairs in a twin study that ascertained twins from a population register [24], earlier age at first hospitalization was considered initial ascertainment.)

Because it can be argued that this method of designating a "proband" twin in the doubly ascertained pairs could maximize the contribution of age at onset in distinguishing probands from concordant and discordant pairs, a parallel set of univariate and multivariate analyses was conducted in which the proband twin in each of the 12 doubly ascertained pairs was designated randomly. The results of these reanalyses were similar to those in which the proband twin was designated on the basis of initial ascertainment; indeed, age at onset played a greater role in discriminating the two groups of probands in these reanalyses.

A manual was developed to assess positive and negative symptoms in these case histories. The manual consists of descriptions of five categories of negative symptoms (affective flattening, alogia, avolition-apathy, asociality-withdrawal, and attentional impairment) and five categories of positive symptoms (delusions, hallucinations, positive formal thought disorder, catatonic motor phenomena, and bizarre behavior). The negative symptom portion of the manual is a modification of Andreasen's interview-based Scale for the Assessment of Negative Symptoms (5) that we adapted for use with case histories. A psychiatrist and a clinical psychologist were trained to use the manual and were instructed to rate each of the randomly ordered 302 case histories for the presence or absence of each of the five negative and five positive symptoms defined in the manual. Interrater reliability for these present-absent ratings for individual symptoms was generally better for positive symptoms (mean kappa=0.75, range=0.70–0.84) than for negative symptoms (mean kappa=0.55, range=0.46–0.64).

Each of the twins was assigned two scores, one for total positive symptoms and one for total negative symptoms, that could range from 0 to 5. The means of the number of negative symptoms and of positive symptoms that each rater judged present for each of the twins were used in the following analyses. Because our scale of negative symptoms includes a rating of asociality-withdrawal, which may be closely related to premorbid social adjustment, we also created a new measure of negative symptoms, negative-4, that excluded this symptom. Additional details concerning the manual and the results of research that has used it have been reported in previous publications (15, 18, 30).

Two new raters, a clinical psychologist and an ad-

TABLE 1. Dimensions of Psychopathology in Monozygotic Proband Twins Concordant and Discordant for Schizophrenia

Measure	Reliabilities (N=151)		Probands From Concordant Pairs (N=69)		Probands From Discordant Pairs (N=82)			
	R[a]	R[b]	Mean	SD	Mean	SD	Z[c]	p[d]
Positive symptoms	0.79	0.88	3.46	1.15	3.23	1.17	1.26	0.209
Negative symptoms	0.74	0.85	2.71	1.26	2.23	1.30	2.19	0.014
Negative-4 symptoms (excludes asociality-withdrawal)	0.66	0.80	1.99	1.10	1.55	1.10	2.32	0.010
Phillips Abbreviated Scale of Premorbid Sexual Adjustment score[e]	0.88	0.94	3.89	2.07	3.13	2.19	2.14	0.016
Zigler-Phillips Social Competence Scale score[f]	0.69	0.81	0.74	0.36	0.89	0.36	2.54	0.006
Venables-O'Connor Scale for Rating Paranoid Schizophrenia score	0.71	0.83	7.22	2.91	8.20	3.26	1.78	0.038
Age at onset (years)			28.2	9.05	31.8	8.49	2.93	0.002

[a]Intraclass correlations for individual ratings.
[b]Intraclass correlations for mean ratings (equivalent to Cronbach's alpha for the mean ratings).
[c]N=151 except for Phillips scale (N=133), Zigler-Phillips scale (N=145), and age at onset (N=149); data missing for some variables in some of the case histories.
[d]Conventional significance levels based on one-tailed Mann-Whitney U tests, except for two-tailed test for positive symptoms. The significance levels based on multistage Bonferroni procedure are as follows: $p<0.10$ for negative symptoms, negative-4 symptoms, Phillips scale, and Venables-O'Connor scale; $p<0.05$ for Zigler-Phillips scale and age at onset.
[e]Higher scores reflect poorer premorbid adjustment.
[f]Lower scores reflect poorer premorbid adjustment.

vanced graduate student in clinical psychology, rated each of the case histories of the 151 proband twins on the Phillips Abbreviated Scale of Premorbid Sexual Adjustment (31, 32) and on the Zigler-Phillips Social Competence Scale (33, 34). Because it has been noted that the Zigler-Phillips scale would be improved by placing more emphasis on social relationships (33–35), the use of both of these scales can be viewed as complementary rather than redundant. There was insufficient information in the case histories to rate them on the Phillips Abbreviated Scale of Premorbid Social-Personal Adjustment (31, 32). The case histories were rated on the two scales for level of functioning before the first documented psychiatric hospitalization (36). The means of the two raters for each of the two scales were used in the following analyses.

The clinical psychologist who 3 years before had rated positive and negative symptoms, and the advanced clinical psychology graduate student who 8 months before had rated premorbid adjustment, subsequently rated each of the case histories of the 151 proband twins on the Venables-O'Connor Scale for Rating Paranoid Schizophrenia (37). The means of the two raters were used in the following analyses.

Several twin studies have examined the relationship between severity and concordance (16, 19, 29), and age at onset has been used as one measure of severity (16, 19). Although it is an imperfect measure of the age at onset of schizophrenia, the only variable that could be rated consistently from the case histories was the proband's age at first documented psychiatric hospitalization. In the majority of cases, this appeared to be the same as the age at onset of psychotic symptoms; in a few cases, age at onset of a clearly described frank psychotic decompensation before hospitalization was used.

RESULTS

The interrater reliabilities for the measures that were rated from the proband case histories are presented in the first section of table 1. As can be seen from the table, the intraclass correlation coefficients (38) for the individual ratings indicate that the reliability of these measures was acceptable. Because all of the following analyses make use of mean ratings based on two raters, the table also presents the intraclass correlation coefficients for these means (equivalent to Cronbach's alpha), which indicate that the reliabilities of the mean ratings were generally excellent.

Univariate Relationships With Concordance

The second section of table 1 presents the relationships between concordance and positive symptoms, negative symptoms, premorbid adjustment, paranoid symptoms, and age at onset for the combined data from all five twin studies; the relationships between concordance and several of these variables for each of the five studies examined individually have already been presented (15, 18). Because the levels of measurement and/or distributions of the scales used in these analyses may violate the assumptions of parametric statistics, nonparametric Mann-Whitney U tests were used to test significance. One-tailed tests of significance were chosen for all measures except positive symptoms because of predictions based on previous family, twin,

and adoption studies (18, 39). A multistage Bonferroni procedure (40) was used to control for multiple tests of significance, and an overall alpha level of $p<0.10$ was used in order to reduce the chance of type II error in the selection of variables to be included in the discriminant analyses (41). As can be seen from table 1, probands from concordant twin pairs had significantly greater numbers of negative symptoms on both measures of negative symptoms, poorer premorbid adjustment on both scales of premorbid adjustment, fewer paranoid symptoms, and earlier ages at onset than probands from discordant pairs. There were no significant differences, however, between probands from concordant and discordant pairs on the measure of positive symptoms.

The concordance rates for male versus female probands for each of the twin studies and for the combined data from all five studies were also compared, but no significant sex differences in concordance were found.

Correlations Among Measures

The Spearman rank-order correlation coefficients among the measures rated from the proband twin case histories were calculated, and two-tailed tests were used to evaluate their significance. Greater numbers of negative symptoms were significantly correlated with poorer premorbid adjustment on both the Phillips ($rho=0.18$, $N=133$, $p<0.05$) and Zigler-Phillips ($rho=-0.26$, $N=145$, $p<0.01$) scales, which were associated with each other ($rho=-0.63$, $N=127$, $p<0.001$). Earlier age at onset was significantly correlated with poorer premorbid adjustment on the Phillips ($rho=-0.41$, $N=131$, $p<0.001$) and Zigler-Phillips ($rho=0.57$, $N=143$, $p<0.001$) scales. Greater numbers of paranoid symptoms were associated with later age at onset ($rho=0.33$, $N=149$, $p<0.001$) and better premorbid adjustment on the Phillips ($rho=-0.21$, $N=133$, $p<0.05$) and Zigler-Phillips ($rho=0.26$, $N=145$, $p<0.01$) scales. Greater numbers of positive symptoms were significantly correlated with greater paranoid symptoms ($rho=0.17$, $N=151$, $p<0.05$) and greater numbers of negative symptoms ($rho=0.20$, $N=151$, $p<0.05$); paranoid symptoms and negative symptoms were, however, not significantly correlated.

The well-known sex differences in age at onset and premorbid adjustment (42) were also present, with male probands having an earlier age at onset ($Z=3.12$, $N=149$, $p<0.01$) and poorer premorbid adjustment on the Phillips ($Z=3.90$, $N=133$, $p<0.001$) and Zigler-Phillips ($Z=3.13$, $N=145$, $p<0.01$) scales than female probands. There were, however, no sex differences in positive symptoms, negative symptoms, or paranoid symptoms.

Discriminant Analyses

Because of the significant interrelationships among the measures we have examined, two discriminant analyses were conducted in order to determine which of the variables most adequately reflect the relationships with concordance that were found. This use of discriminant analysis, which has been called "descriptive" discriminant analysis, must be distinguished from predictive discriminant analysis, which is concerned with the classification of cases into groups (43). We have conducted descriptive discriminant analyses because the aim of our analyses is to identify which measures have at least partially independent associations with concordance, not to develop a method for classifying probands into concordant and discordant groups (this is accomplished by whatever method of clinical assessment is used in a twin study).

TABLE 2. Descriptive Discriminant Analyses for Monozygotic Proband Twins Concordant Versus Discordant for Schizophrenia

Analysis, Step, and Variable	Partial F-to-Enter	p	F-to-Remove
Stepwise entry of variables			
1: Zigler-Phillips scale	7.07	0.01	
2: Venables-O'Connor scale	1.98	0.16	
3: Negative symptoms	1.78	0.18	
Age at onset	1.06	0.31	
Phillips scale	0.02	0.89	
F-to-remove after entry of all variables			
Venables-O'Connor scale			1.71
Negative symptoms			1.69
Zigler-Phillips scale			1.17
Age at onset			1.06
Phillips scale			0.03

As is typically done, those variables which discriminated concordant and discordant probands in the univariate analyses were used to discriminate concordant and discordant probands in the discriminant analyses (44, 45). In descriptive discriminant analysis, a stepwise analysis using Wilk's lambda as the criterion for variable selection is most often reported (43, 44). The top panel of table 2 presents a summary of the results of this type of discriminant analysis. As can be seen from table 2, three variables—the Zigler-Phillips Social Competence Scale, the Venables-O'Connor Scale for Rating Paranoid Schizophrenia, and negative symptoms—each entered the analysis with a partial F-to-enter greater than 1.5. Age at onset and the Phillips scale were not selected in the analysis, indicating that the unique contribution of these two variables was insufficient to provide further discrimination between concordant and discordant probands. It should be noted that on the basis of the univariate analyses presented in table 1, age at onset would be expected to enter the discriminant analysis on the first step. This did not occur because the discriminant analyses were conducted with only those probands for whom there were no missing data for any of the five measures ($N=125$), a necessarily smaller sample than that used for each of the measures in the univariate analyses.

But it has recently been argued that, contrary to popular belief, a stepwise analysis is not an appropriate method of selecting and ordering the importance of

variables in a discriminant analysis (43). A more effective method of examining the contribution of each of the variables to discriminating concordant and discordant probands is therefore presented in the bottom panel of table 2. This method is based on the F-to-remove of the variables after all have been entered into the analysis (43, 44). These F-to-remove values reflect the *unique* discriminating power of each of the variables in the set. The variable with the largest F-to-remove makes the greatest contribution to group separation above and beyond that made by the other variables (44). The rank order of these F values therefore indicates the relative importance of each variable in contributing to group separation. On the basis of the F-to-remove values presented in the bottom panel of table 2, paranoid symptoms, negative symptoms, and the Zigler-Phillips measure of premorbid social competence are, in this order, the variables that make the greatest unique contributions to discriminating concordant and discordant probands.

In both of the discriminant analyses we have conducted, negative symptoms, premorbid social competence, and paranoid symptoms made the greatest contribution to discriminating concordant and discordant probands. The order of these three variables differed between the customary stepwise analysis and the more appropriate analysis of the unique contribution that each variable makes to discriminating the two groups of probands, but the same three variables were selected as making the greatest contribution to group discrimination. It is important to emphasize the consistency of the results of these two different analyses and to recognize that variable order in discriminant analysis is sample-specific and generalizability cannot be assumed (43).

DISCUSSION

On the basis of univariate analyses, proband twins from concordant pairs were found to have significantly greater numbers of negative symptoms, poorer premorbid adjustment, fewer paranoid symptoms, and earlier ages at onset than probands from discordant pairs. Because of interrelationships among these variables, descriptive discriminant analyses were conducted in order to determine which of these variables made the greatest unique contribution to discriminating concordant from discordant probands. In two different approaches to discriminant analysis, negative symptoms, premorbid social competence, and paranoid symptoms (a type of positive symptom) each contributed to the discrimination between concordant and discordant probands. Regardless of whether these associations with concordance reflect the genetic predisposition to schizophrenia or nongenetic familial factors, these results provide support for Strauss et al.'s suggestion (1) that these three types of symptoms reflect three different functional processes in the development of schizophrenia.

Additional support for the partial independence of two of these three dimensions has been provided by the results of confirmatory factor analyses of the positive and negative symptom data from all of the probands and co-twins diagnosed as schizophrenic (N= 220) in these five twin studies. In these analyses, the best fit to the data was provided by a model of two independent underlying dimensions reflected in positive and negative symptoms (M.F. Lenzenweger, R.H. Dworkin, E. Wethington, unpublished data).

It must be acknowledged that the case histories on which our analyses are based were not prepared with this research in mind and that they may therefore omit important symptoms. This may have been especially true with respect to negative symptoms, which until recently did not receive as much attention as positive symptoms. Fortunately, extensive case histories from one of the twin studies included in our analyses have recently been reanalyzed, and the results are consistent with our conclusions about positive and negative symptoms and genetic influences in schizophrenia (46–48). Our results are also consistent with previous studies of the relationship of genetic influences in schizophrenia to premorbid adjustment, severity, and paranoid symptoms (18, 39). But it must be emphasized that the multivariate approach taken in this study extends the findings of prior univariate research in which it was not possible to examine the extent to which these different dimensions had partially independent or overlapping relationships with genetic influences.

An additional methodological consideration is that we have pooled patients from different studies in our analyses. Ideally, separate multivariate analyses should have been conducted for each twin study, but this was precluded by small sample sizes. Our results are based on reanalyses of combined data from five different twin studies conducted in four countries over a span of more than 30 years. It is important to recognize that the original investigators committed a great deal of time and effort to assembling this unique set of data, and it is unlikely that many new twin studies of schizophrenia will be undertaken.

A variety of models have been proposed to account for relationships between the genetic predisposition to develop schizophrenia and negative symptoms, premorbid adjustment, and paranoid symptoms (8, 18, 39, 46, 47). The results of our analyses suggest that negative symptoms and poor premorbid social adjustment are associated with either a genetic or familial liability to develop schizophrenia. The results of an adoption study (49) suggest that this liability is more likely to reflect genetic influences, at least with respect to premorbid social adjustment. Because paranoid symptoms are more common in discordant probands, they would seem to reflect a pathophysiological process (e.g., viral infection, birth complications) that is associated with less of a genetic (or familial) liability to develop schizophrenia. The data, however, do not address the important question of the specificity of these processes to the development of schizophrenia; it has

been argued that at least one of the processes we have examined, premorbid social adjustment, is as relevant to other mental disorders as it is to schizophrenia (35, 50).

Appreciable evidence suggests that both negative symptoms and disordered social relationships play an important role in the longitudinal course of schizophrenia and in its outcome (50–52). Paralleling these findings, our data suggest that both negative symptoms and poor premorbid social adjustment are associated with an increased genetic liability to develop schizophrenia and that these relationships are at least partially independent. The most important implication of our results is the support they provide for a longitudinal (and multidimensional) approach to schizophrenia, an approach in which the development of social relationships and the unfolding of positive and negative symptoms are studied in combination.

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Comparison of MRI and CT Scans in a Group of Psychiatric Patients

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The authors compared the results of computerized tomography (CT) and magnetic resonance imaging (MRI) scans of 16 psychotic patients with various diagnoses whose neurologic examinations suggested structural brain abnormalities. Blind readings showed a high concordance of findings, including ventricle-to-brain ratios, although MRI appeared superior in visualizing midline structures and identifying atrophic changes. Because it requires no ionizing radiation, MRI allows multiple studies of the same patient, study of family members, and recruitment of unbiased samples of control subjects. Use of MRI may help address questions regarding the specificity and prevalence of brain abnormalities observed with CT in psychotic patients.

(Am J Psychiatry 1988; 145:1084–1088)

In the last decade, a variety of new or enhanced brain imaging techniques that promise to add relevant information on brain structure and function in patients with psychiatric disorders have become available. These techniques include X-ray computerized tomography (CT), measurements of regional cerebral blood flow using xenon-133, computer-assisted EEG, positron emission tomography (PET), single photon emission computerized tomography (SPECT), and nuclear magnetic resonance imaging (MRI).

Of these techniques, only CT has been studied in a substantial number of psychiatric patients, and to date, more than 70 studies of CT in samples of psychotic (mostly schizophrenic) patients have been reported. These studies suggest that certain subgroups of schizophrenic patients may exhibit structural abnormalities of the brain. Numerous studies (1–9) have reported a greater prevalence of lateral ventricular enlargement in schizophrenic subjects than in control samples. Other studies report enlargement of the third ventricle (10–14) or cerebellar vermis atrophy (13, 15, 16) in schizophrenic patients. Reversal of the normal pattern of asymmetry has also been reported in a subgroup of severely ill chronic schizophrenic inpatients (17–20).

However, the validity and specificity of these findings have been questioned. Several controlled studies have found no evidence of ventricular enlargement (21–23) or reversed cerebral asymmetry (6, 24–26) in schizophrenic patients. Other studies have reported that ventricular enlargement is as common in patients with bipolar disorder (13, 27) or delusional depression (27, 28) as it is in patients with schizophrenia.

These findings leave open the question of the relationships between psychosis and structural abnormalities of the brain. The disparity of these findings and the lack of specificity across diagnoses may be due, in part, to methodologic differences between studies—for example, different diagnostic criteria; different measurement techniques to assess ventricular size and cortical area; heterogeneity within the syndromes studied; and differences in age, inpatient status, duration and severity of illness, response to and duration of treatment, family history, and history of birth complications in the samples studied (29). However, with imaging techniques that involve the use of ionizing radiation, such as CT, the greatest limitations in interpreting the results are finding adequate control groups and performing repeated measures to gauge the relationship between the abnormalities observed and the natural history of the disease or the effects of treatment.

MRI may have special advantages in this regard, as it appears quite safe, involving no ionizing radiation. Thus, control groups with other illnesses and matched normal control subjects chosen from unbiased populations can be studied. In addition, patients can be studied multiple times during different stages of their illnesses and while receiving different medications.

Furthermore, proton nuclear magnetic resonance imaging (the only MRI technique in practical use for psychiatric research to date) yields excellent gray/white matter resolution, has no bone artifacts, and provides potential imaging in any plane (30). Thus, it has the capability of defining those structural aspects of brain which might be most relevant to chronic psychosis.

To our knowledge, only six studies applying MRI to

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subjects with psychotic disorders have yet been published (31–36). These studies contained small numbers of subjects and reported 1) significantly smaller frontal lobes, cerebra, and crania on midsagittal sections in schizophrenic patients (32), 2) thicker anterior and middle corpus callosum in female schizophrenic patients (36), 3) no abnormality in cerebellar vermis size or in height of the fourth ventricle on midsagittal sections in schizophrenic patients (33), 4) no abnormality in measures of linear or area brain morphology on coronal slices but a possible increase in T_1 proton relaxation time in white matter bilaterally of both the frontal and temporal lobes of schizophrenic patients (34, 35), and 5) increased T_1 times in frontal and temporal areas bilaterally in patients with bipolar disorder, most of whom were in the depressed phase (31).

Despite the large literature on CT findings in psychotic disorders, in only one study of MRI (34) did the authors comment on the results of CT scans in their subject sample. Furthermore, even these authors made no explicit comparison of CT and MRI findings by case. Rather, they noted only that, in general, MRI appeared to provide superior detail in imaging subcortical nuclei. Thus, there are as yet no grounds to determine if MRI and CT are comparable or complementary techniques for the study of psychoses.

As part of a preliminary study of the applicability of MRI to the study of psychosis, we performed MRI studies of psychotic patients who had no known neurologic disease but whose CT scans indicated likely structural abnormalities of the brain. We subsequently compared the results of MRI and CT to answer the following questions:

1. Are the findings from CT also apparent from MRI? That is, is MRI sensitive to the same abnormalities in psychotic patients as CT?
2. Are there findings from MRI in addition to those apparent from CT? That is, does MRI have a special advantage in studying psychotic patients in that it detects abnormalities not observed with CT?

We report on the results of these comparisons.

METHOD

Sixteen hospitalized psychotic patients participated in the study after informed consent was obtained. A subject was included if, in the absence of known neurologic disease, abnormalities were apparent from a CT scan of the head or from EEG. Neurologic examinations were performed by a staff neurologist (S.P.F.). EEGs were performed at McLean Hospital and read by a staff neurologist-encephalographer. Subjects who had histories of head trauma with loss of consciousness or any neurologic disease, including CNS consequences of other medical illnesses, were excluded. Pregnant women and subjects with head plates, cardiac pacemakers, or other metallic prostheses were also excluded.

DSM-III diagnoses were ascertained through interview by a staff psychiatrist and were verified through chart review by a second psychiatrist (P.E.K.). Nine patients were diagnosed as schizophrenic; three patients had bipolar disorder, manic phase; three patients had schizoaffective disorder (two manic, one depressed); and one patient had borderline personality disorder with transient psychotic episodes. The mean duration of illness was 5.4 years; the range was 0.5 to 14.0 years. The patients were receiving various antipsychotic and thymoleptic medications (including lithium salts) at the time of study. Fourteen patients were right-handed, and two were left-handed.

Standard hydrogen-1 proton images were obtained through the Massachusetts General Hospital MRI facility with a Teslacon 0.6-T superconductive magnet, a commercially produced apparatus. Multislice imaging was performed in the transaxial and coronal planes, with pulse sequences that yielded T_1-weighted and T_2-weighted "stacks" of 12–15 0.75-cm-thick images. For the T_1-weighted images, a repetition time (TR) of 1500 msec, an inversion time (TI) of 550 msec, a time to echo (TE) of 25 msec, and two signal averages were used. For T_2-weighted images, the TR was 2000 msec and multiple echo times (TE—60 and 120 msec) were used. The images were reconstructed and photographed to produce radiographic "hard copy" film.

Each patient received a CT scan (Toshiba TCT20A scanner). The scanner yielded about 12 slices for each patient. A scan was not included in the study if it had indications of movement artifacts or any other procedural problems. All slices were evaluated on the "hard copy" printout.

The CT scan and MRI films were read by a neuroradiologist (F.B.) who was blind to the origin of the imaging study. Ventricle-to-brain ratios (VBRs) were calculated after the body of the ventricle was measured at the cella media level with a Bioquant System IV Image Analysis System (R&M Biometrics, Nashville, Tenn.). Linear regression analysis was performed and the correlation coefficient (r) was obtained for the correlation between the VBRs based on the CT and MRI scans.

RESULTS

Comparisons of the radiologist's blind readings of the MRI and CT scans of the 16 subjects are summarized in table 1.

For seven subjects (patients 3, 6, 9, 10, 11, 12, 16) the CT scan and MRI readings were identical. The MRI findings for subject 1 implied evidence of a neuroanatomical abnormality, and the CT scan results did not. For eight subjects (patients 2, 4, 5, 7, 8, 13, 14, 15) the CT scan and MRI findings were each read as abnormal but in different ways. Even in these subjects there was agreement on most findings, and the differences were minimal.

MRI showed superiority to CT in visualization of midline structures and detected a possible cavum sep-

TABLE 1. Findings From CT, MRI, EEG, and Neurologic Examinations of 16 Psychotic Patients

Subject	Age (years)	Sex	*DSM-III* Diagnosis	Findings			
				CT	MRI	EEG	Neurologic Examination
1	19	M	Schizoaffective disorder	Normal	Cavum septum pellucidum	Background slowing posteriorly, greater on right	Proximal chorea attributable to neuroleptics
2	22	M	Schizophrenia	Large fourth ventricle; left ventricle larger than right	Large fourth ventricle	Normal	Normal
3[a]	26	M	Bipolar disorder	Normal	Normal	Frequent slow wave activity, greater in right mid- and anterior temporal region	Normal
4	22	M	Bipolar disorder	Right hemisphere larger than left; temporal horns visualized	Frontal atrophy; right temporal increase in T_2 time	Normal	Right Hoffman's sign
5	35	F	Schizophrenia	Slightly large fourth ventricle; temporal horns visualized	Right temporal horn larger than left; coarctation of right frontal horn; bifrontal atrophy	Abnormal bursts of high-voltage activity in left temporal region	Normal
6	23	M	Schizophrenia	Enlarged temporal horns with ventricular dilatation; enlarged cisterna magna	Enlarged temporal horns with ventricular dilatation; enlarged cisterna magna	Normal	Normal
7	16	F	Borderline personality disorder	Enlarged temporal horns	Enlarged temporal horns; right posterior temporal tissue loss	Persistent background slowing, most prominent in left temporal area	Normal
8	19	M	Schizoaffective disorder	Enlarged temporal horns; wide interhemispheric fissure	Enhanced left thalamic T_2 and periaqueductal T_2 time	High-voltage sharp and slow activity and occasional spike wave complexes anteriorly	Normal
9	26	M	Schizophrenia	Enlarged ventricles	Enlarged ventricles	Intermittent background slowing, most prominent bitemporally	Left hyperreflexia; excessive mirror movements
10	21	M	Schizophrenia	Enlarged left frontal horn	Enlarged left frontal horn	Normal	Normal
11	33	M	Schizophrenia	Enlarged ventricles	Enlarged ventricles	Normal	Normal
12[a]	23	F	Schizophrenia	Normal	Normal	Generalized slowing	Hyporeflexia
13	26	M	Schizophrenia	Enlarged ventricles	Enlarged ventricles and right temporal horn	Normal	Normal
14	26	M	Schizophrenia	Enlarged ventricles	Enlarged ventricles and right temporal horn	Bursts of sharp and slow activity	Normal
15	55	F	Bipolar disorder	Left frontal horn larger than right; bifrontal tissue loss; enlarged temporal horns	Left frontal horn larger than right, bifrontal tissue loss	Generalized slowing	Normal
16	31	M	Schizoaffective disorder	Enlarged ventricles	Enlarged ventricles	Long bursts of high-voltage slow and sharp wave activity	Hyporeflexia

[a]Left-handed. Other subjects were right-handed.

tum pellucidum (patient 1) not apparent on the CT scan. In addition, MRI revealed foci of prolonged T_2 relaxation times in the right temporal lobe of one subject (patient 4) and thalamus of another (subject 8). However, the clinical significance of prolonged T_2 relaxation times is uncertain. Finally, the capacity of MRI to provide coronal cuts revealed atrophic changes in several subjects (patients 4, 5, 7) that were not apparent in the transaxial images.

In all cases, the differences between the CT and MRI readings involved subtle or uncertain findings. In no case of disagreement were the abnormalities observed felt to be clinically relevant. None of the findings from CT or MRI explained clinical observations or led to a change in treatment.

The range of VBRs calculated from the CT scans was 0.031 to 0.123, and for MRI it was 0.040 to 0.131. The mean±SD VBRs for the CT and MRI scans were remarkably similar: 0.81±0.31 and 0.81±0.27, respectively. Regression analysis showed a correlation between the VBRs based on CT and MRI of $r=0.695$ ($p<0.005$). The several patients with the most extreme (large and small) VBRs according to CT scan also had the most extreme VBRs according to MRI. Some individual patients had VBRs that varied between CT and MRI, but these differences appeared to be attributable to differences in the angulation of the two scans.

DISCUSSION

In this study, proton MRI offered additional but subtle information and provided no dramatic clinical findings beyond those observed with CT. This is especially important since the study sample was chosen to reflect patients with likely structural abnormalities of the brain. Conversely, all CT findings felt to be more than suggestive of abnormality were also observed with MRI.

Therefore, two tentative conclusions can be drawn from the results of this study. Our results suggest that studies of patients by means of CT and proton MRI will yield similar or equivalent findings on measures such as ventricular size, hemispheric asymmetry, or brain atrophy, particularly on a group basis. However, in studies of large numbers of patients, MRI may detect occasional abnormalities not visible with CT scanning. In particular, the further study of abnormalities of T_1 and T_2 relaxation times, which may indicate underlying physicochemical abnormalities of brain tissue (30) and can only be observed by means of MRI, would be worthwhile. This is especially true since studies of bipolar illness (31) and Alzheimer-type dementia (37) suggest abnormalities of T_1 times in patients with these disorders.

Finally, given these results, proton MRI may successfully address questions about structural abnormalities of the brain left unresolved by CT studies. MRI's utility in this regard is most strongly suggested by the observation that the controversies regarding the interpretation of CT scans of psychotic patients most often involve the questions of whether the control groups are adequately unbiased and whether the findings, such as enlarged ventricles or atrophy, reflect static properties of brain or reversible changes due to drug treatment or poor hydration (29, 38). Since MRI does not involve ionizing radiation, it allows multiple studies of patients over time, the study of relatives of patients, and the recruitment of unbiased control samples. Thus, where it is available, it may be the preferred technique for studying anatomic questions about psychiatric patients.

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Neuroanatomical Abnormalities in Obsessive-Compulsive Disorder Detected With Quantitative X-Ray Computed Tomography

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New brain imaging techniques may provide evidence for a biological basis for severe psychiatric disorders. The authors used quantitative X-ray computed tomography (CT) to analyze the brain volume of 10 male patients with severe primary obsessive-compulsive disorder and 10 healthy male control subjects. Caudate nucleus volume in the patients with obsessive-compulsive disorder was significantly less than that of control subjects, but lenticular nuclei, third ventricle, and lateral ventricle volumes did not differ between these two groups, and no abnormal asymmetry of bilateral structures was detected. These findings support other evidence of involvement of the caudate nucleus in obsessive-compulsive disorder.

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Abnormalities of cerebral anatomy, histology, metabolism, and chemistry have been detected in a variety of psychiatric disorders. These abnormalities may provide clues to the pathophysiology and etiology of an illness and have been used in some cases to develop a rationale for treatment. The recent development of noninvasive radiological techniques for imaging neuroanatomy in living subjects allows us to study disorders with onset in younger age groups where too few cases have been collected for autopsy series.

Obsessive-compulsive disorder was considered relatively rare until its prevalence was recognized to be 2% of the general population (1). It is a chronic debilitating disorder (*DSM-III*, pp. 124–126) with onset typically in adolescence and young adulthood. Patients' lives are disrupted by irrational compulsions to wash or check excessively, or they are troubled by recurrent irrational thoughts (e.g., that they have just caused someone's death). Patients recognize these thoughts and habits as senseless but do not regularly seek treatment; thus, the disorder is underrepresented at clinical centers. Evidence for a biological basis for this disorder (2–4) includes selective response to psychopharmacologic agents, a higher rate of concordance in monozygotic than in dizygotic twins (4, 5), and association with epilepsy and brain trauma (6), but the association of obsessive-compulsive disorder with movement disorders, which indicates an association with basal ganglia lesions (7), is most striking. A dramatically high rate of obsessive-compulsive disorder is found in patients with Gilles de la Tourette's syndrome as well as in the families of such patients (8, 9). Inheritance patterns in families with Tourette's syndrome and obsessive-compulsive disorder support the hypothesis of a highly penetrant, sex-influenced, autosomal dominant trait (9). Obsessive-compulsive disorder was associated with the 1920s encephalitis lethargica epidemic (10), Sydenham's chorea, and Meige's syndrome (7). Abnormalities of neurotransmitters (11), cerebral metabolism (12), probable response to leukotomy (4), and response to pharmacotherapy (13) also suggest a biological basis for obsessive-compulsive disorder. Finally, relief of obsessive-compulsive disorder after psychosurgery in which the orbital frontal cortex and anterior cingulum are interrupted has particularly pointed to an abnormal frontal lobe-basal ganglia interaction in obsessive-compulsive disorder.

The advent of computed X-ray tomography (CT) has allowed in vivo studies of neuroanatomical features of obsessive-compulsive disorder in living subjects (14). Techniques of quantitative volumetric analysis (15, 16) have allowed a volumetric analysis of cerebral anatomy in psychiatric disease (17). In this paper we will report the first study of brain morphometrics using quantitative volumetric CT in obsessive-compulsive disorder.

METHOD

Subjects

Ten male patients (mean age=20.7±2.1 years, range=17–24 years) with onset of severe primary obsessive-compulsive disorder before age 18 were re-

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cruited as part of an ongoing study of pharmacologic therapy for childhood-onset obsessive-compulsive disorder (13). Patients were referred by mental health care professionals and primary care physicians throughout the United States and were screened by at least two psychiatrists at the Clinical Center of the National Institutes of Health, Bethesda, Md.

Patients met *DSM-III* criteria for severe primary obsessive-compulsive disorder, and their symptoms had persisted for at least 1 year at some time during their illness. Inclusion criteria were childhood onset (before age 17) and rituals and/or repetitive thoughts deemed unreasonable by the patient, experienced as distressful, and resulting in nontrivial interference in home, school, or interpersonal functioning in the absence of another mental disorder. Secondary depression, defined as affective symptoms occurring after the onset of obsessional illness, was not an exclusion criterion. However, none of the patients was depressed at the time of examination (their mean score on the 22-item Hamilton Rating Scale for Depression=7.9, range=4–13). All subjects underwent a complete psychiatric and medical evaluation, and families were interviewed. Results of neurological examination of these subjects were normal.

Ten healthy male control subjects (mean age=23.7±2.6 years, range=21–28 years) were also studied. All were enrolled in the Longitudinal Study of Brain Function in Healthy Aging conducted by the Laboratory of Neurosciences, National Institute on Aging (National Institutes of Health protocol 80 AG-26). The screening method has been described previously (18). They had no history of systemic illness, psychiatric disorder, or alcohol or drug abuse and were free of evidence of illness after physical examination and a screening laboratory evaluation. None was taking medication.

The age and educational levels of the male patients and control subjects were comparable, although the mean age of the control subjects was greater than that of the patients because no control subjects under age 18 can be scanned under current radiation guidelines.

All patients and control subjects gave written informed consent after the purpose of the study, testing procedures, and associated risks were discussed with them.

CT Scanning

Noncontrast CT imaging was performed by using a General Electric 8800 CT/T scanner (General Electric Corp., Milwaukee), for which full width at half maximum equaled 1 mm. Images were obtained parallel to the externally defined inferior orbitomeatal line. Each slice was 10 mm thick, and the interslice spacing was 7 mm. The scanner was standardized daily by using an internal program and a water phantom set to a mean CT density of 0 Hounsfield units (HU), and phantoms of differing CT densities were scanned periodically.

CT data were stored in digital form on magnetic tape and were analyzed on a PDP 11/34 computer (Digital Equipment Corp., Maynard, Mass.) with a DeAnza Picture Display Monitor (Gould, Inc., Fremont, Calif.).

Analytic Methods

The semiautomated method used in the analysis is described in detail elsewhere (15–17, 19). Each CT slice was displayed on the television monitor, and regions of interest were outlined by using a digitalizing graphics tablet and a light pen. Regions of interest for the lateral and third ventricles, right and left caudate nuclei, and lenticular nuclei were outlined on each slice in which the structures were seen. The number of pixels in each region of interest was computed. Volumes of intracranial structures were derived by summing the number of pixels of a measure of interest across slices and multiplying by the pixel area (0.0064 cm^2) and the interslice distance (0.7 cm). The total numbers of intracranial pixels were determined for a 49-mm horizontal central segment (15), beginning with the first slice on which the base of the third ventricle was seen, by using an automatic edge-finding procedure (15); for the remaining slices they were determined by outlining the intracranial area as already described.

Absolute volumes for the cerebral ventricles and subcortical nuclei were expressed as percentages of the individual 49-mm intracranial segment to adjust for variation of head size.

All scans of both patients and control subjects were analyzed by a single rater (J.S.L.) who was blind to diagnosis. The coefficients of variation for intrarater reliability ranged from 8.4% to 14.5%. Interrater reliability (between J.S.L. and S.E.S.) for these measures was tested by using an interclass correlation coefficient (ICC) (20). The ICCs for the regions of interest ranged from 0.74 to 0.97, and all were significant at $p<0.005$. The volumes of the right and left thalami were examined in a similar fashion, but they were excluded because satisfactory interrater reliability could not be achieved.

Statistical Analysis

The volumes of the 49-mm central brain segment, total intracranial volume, and head-size-corrected third ventricle volume were compared by using Student's t test (21). Repeated measures analyses of variance (20) were used to test for group differences in the bilateral structures (2 by 2, Group by Side). The Group-by-Side interactions were tested for possible abnormal asymmetries of the obsessive-compulsive disorder patient group. A folded F statistic (21) was used to test homogeneity of variance.

The major hypotheses were that there would be group (diagnosis) effects on intracranial volumes, structural asymmetry of paired structures, and Group-by-Side interactions. Thirteen comparisons were made,

TABLE 1. Computed Tomographic Brain Volumes for 10 Patients With Obsessive-Compulsive Disorder and 10 Control Subjects

Volume Measured	Control Subjects		Obsessive-Compulsive Patients		F or t	df	p
	Mean	SD	Mean	SD			
Absolute volumes (ml)							
Total intracranial segment	1268.41	137.97	1390.03	156.84	t=1.84	18	n.s.
49-mm central segment	783.20	57.44	840.94	98.73	t=1.60	18	n.s.
Volumes as proportions of 49-mm central segment							
Ventricles							
Third	0.12	0.04	0.12	0.06	t=0.34	18	n.s.
Lateral							
Right	1.17	0.98	1.25	0.89			
Left	0.96	0.55	1.29	0.94			
Group main effect					F=0.30	1, 18	n.s.
Side main effect					F=0.50	1, 18	n.s.
Two-way interaction					F=1.06	1, 18	n.s.
Subcortical nuclei							
Caudate							
Right	0.45	0.08	0.34	0.08			
Left	0.47	0.09	0.35	0.09			
Group main effect					F=12.56	1, 18	0.003[a]
Side main effect					F=0.54	1, 18	n.s.
Two-way interaction					F=0.03	1, 18	n.s.
Lenticular nucleus							
Right	0.63	0.12	0.70	0.26			
Left	0.65	0.13	0.60	0.21			
Group main effect					F=0.40	1, 18	n.s.
Side main effect					F=0.06	1, 18	n.s.
Two-way interaction					F=0.32	1, 18	n.s.

[a]Bonferroni correction for multiple hypotheses held an overall $p<0.05$.

with an experiment-specific error rate of $p<0.05$ (22). Individual inferences were made at $p<0.003$.

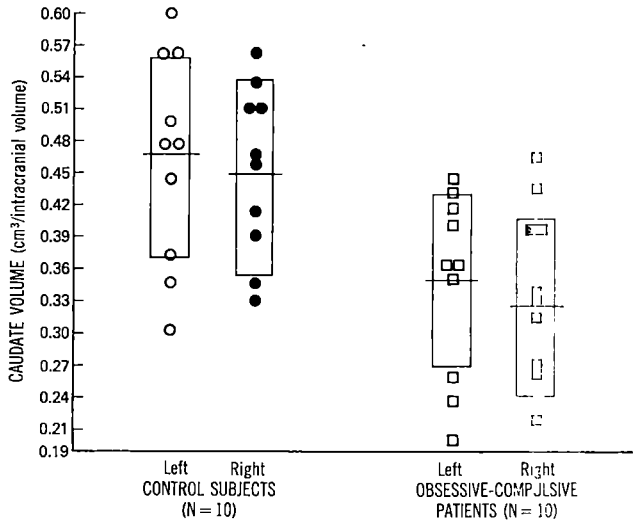
RESULTS

The volumes of intracranial structures are presented in table 1 and figure 1. The only significant group difference was a smaller volume of the caudate nuclei in the patient group (figure 1). No asymmetry of the volumes of the caudate was noted. No group differences in the means or variances of the volumes of the third ventricle, lateral ventricles, or lenticular nuclei were detected.

DISCUSSION

Quantitative CT scanning in a group of young men with childhood-onset obsessive-compulsive disorder and a group of healthy male control subjects showed bilaterally smaller caudate nuclei in the patients with obsessive-compulsive disorder. By studying adults with obsessive-compulsive disorder, we avoided confounding differences in rates of brain development with permanent structural differences in the two groups. Furthermore, carefully selected healthy control subjects were available, whereas healthy pediatric control subjects are unavailable for CT studies. Although the mean age of patients was 3 years less than that of the

FIGURE 1. Distribution of Right and Left Caudate Volumes in Patients With Obsessive-Compulsive Disorder and Control Subjects



control subjects, all patients were at least 17 years old. The similarity in sizes of total intracranial and 49-mm central segment volumes between patients and control subjects suggests that the patients had probably reached adult structural brain development.

Supportive evidence for the significance of the detected abnormalities in the caudate nuclei include the links between movement disorders, particularly of the

choreiform type (7), and obsessive-compulsive disorder in symptoms (2) and familial occurrence (8, 23). Cummings and Frankel (7) proposed a hypothesis linking basal ganglia dysfunction with the aberrant simple motor programs that result in the vocal and motor tics of Gilles de la Tourette's syndrome and with the more complex motor programs that result in obsessive-compulsive symptoms.

Obsessive-compulsive symptoms have been noted in association with Meige's syndrome (24). In one case of Meige's syndrome (25) severe gliosis and neuronal loss were described in the dorsal caudate and putamen. Neuropathologically, the caudate was abnormally flattened.

Additional support for caudate involvement in obsessive-compulsive disorder comes from in vivo metabolic imaging using positron emission tomography (PET). Greater regional cerebral metabolic rates for glucose were detected in both caudate nuclei of patients with obsessive-compulsive disorder than in those of control subjects and patients with unipolar affective disorder (12). Cerebral metabolic abnormalities in obsessive-compulsive disorder were limited to the caudate nuclei and the left orbital gyrus (12).

Corticostriate fibers projecting from the frontal cortex to the dorsolateral and ventromedial sectors of the caudate nucleus have been hypothesized (26) to be part of a behaviorally important neural circuit linking multiple functionally related cortical regions, the striatum, the pallidum, the thalamus, and the frontal cortex. Schneider (27) has proposed that interference with the sensory information gating function of the basal ganglia may result in profound behavioral disturbances. The coexistence of obsessive-compulsive symptoms in many disorders where basal ganglia pathology has been detected (24) supports the relationship between these structures and obsessive-compulsive disorder.

Although abnormalities in size of a structure may artifactually result in group differences in measured regional cerebral metabolic rate for glucose due to partial voluming in PET scanning (28), the smaller caudate nuclei detected in this study would reduce recovery of brain radioactivity (the fraction of the true radioisotope concentration measured in the PET image). This tendency is counter to the regional cerebral metabolic rate for glucose elevation observed in the caudate of the patients with obsessive-compulsive disorder; thus, the findings of Baxter et al. (12) cannot be accounted for by the volume differences presented here.

We have not confirmed the report of Behar et al. (14) of ventricular enlargement in pediatric patients with obsessive-compulsive disorder. That report, however, used planimetric ventricle size, and volumetric measurements of ventricle size have been demonstrated (29) to be more sensitive than planimetric measurements to group differences in size. Behar et al. also used a combined analysis of male and female patients with obsessive-compulsive disorder and control subjects whose CT scans were obtained for health-related reasons, unlike the healthy volunteer control subjects used for our current study. CT scans of 10 patients with mixed childhood-onset and adult-onset obsessive-compulsive disorder (30) did not reveal ventricular enlargement or cortical atrophy compared with age- and gender-matched control subjects.

CONCLUSIONS

In summary, several lines of evidence point to basal ganglia involvement in obsessive-compulsive disorder, particularly with respect to basal ganglia-frontal lobe relationships. Ten men with childhood-onset obsessive-compulsive disorder had significantly smaller caudate nuclei bilaterally than did healthy control subjects. This neuroanatomical abnormality is consistent with a neurobiological etiology of childhood-onset obsessive-compulsive disorder. Additional research is warranted to investigate the nature of basal ganglia-frontal lobe impairment as an etiologic feature in obsessive-compulsive disorder.

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Anterior Pituitary, Adrenal, and Gonadal Hormones During Cocaine Withdrawal

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Plasma luteinizing hormone (LH), prolactin, testosterone, and cortisol levels were determined in 16 patients after hospital admission for cocaine abuse, during the course of 4 weeks of hospitalization, and before discharge. Hyperprolactinemia was found at admission (mean±SD, 27.5±10.2 ng/ml) and persisted until discharge (mean±SD, 28.7±10.8 ng/ml). Plasma LH, testosterone, and cortisol levels were within normal limits. These findings suggest that persistent elevation of plasma prolactin levels after cocaine withdrawal may reflect a chronic cocaine-induced derangement in neural dopaminergic regulatory systems.

(Am J Psychiatry 1988; 145:1094–1098)

Cocaine use is sometimes initiated to facilitate libidinal drive (1), but chronic cocaine abuse causes derangements in reproductive function (2). Impotence and gynecomastia have been reported by men who chronically abuse cocaine (3). There are also reports of persistent abnormalities in reproductive function in men after abstinence from cocaine (4). Cocaine abuse also has adverse effects on reproductive function in women, including derangements of menstrual cycle function, galactorrhea (4), amenorrhea, and infertility (5). There is also evidence that women who chronically use cocaine during pregnancy may have children who are at high risk for development of congenital malformations and perinatal mortality (6).

We have been unable to locate any controlled systematic studies of the anterior-pituitary-gonadal or anterior-pituitary-adrenal axis in cocaine abusers. However, there have been three studies which indicate that plasma prolactin levels may be altered by chronic cocaine abuse. Gawin and Kleber (7) found decreased prolactin levels in men and women who were studied in outpatient clinic settings for the treatment of cocaine abuse. Dackis and Gold (8) found an increase in plasma prolactin levels in men treated in inpatient facilities for cocaine abuse and that their increased prolactin levels were significantly higher than those in age-matched normal men. Cocores et al (4) reported occurrence of hyperprolactinemia as well as self-reports of sexual dysfunction in 7 of 10 cocaine abusers.

The purpose of this study was to measure anterior pituitary, adrenal, and gonadal hormones in plasma samples obtained from patients shortly after admission to the hospital for treatment of cocaine abuse and to evaluate basal hormone levels during the course of hospitalization and before discharge.

METHOD

Sixteen patients, 14 men between the ages of 20 and 40 years and two women aged 23 and 26 years, provided informed consent for participation in this study. All patients were admitted to McLean Hospital for treatment of cocaine dependence. Although some patients reported social use of alcohol and/or occasional use of cannabis compounds, no patient had a diagnosis of psychoactive substance abuse or dependence other than cocaine dependence. No patient had any axis I diagnosis based on criteria specified in *DSM-III-R*, and none reported any history of prior episodes of mental illness other than cocaine abuse and dependence.

Two studies were carried out with this patient cohort. Table 1 shows the sex, age, amount of cocaine self-administered, duration of use, and primary mode of self-administration for the 14 men and two women. The amount of self-administered cocaine ranged from 1 to 7 g/day or 1.5 to 8 g/week. The duration of cocaine use ranged from 1 to 10 years. The primary mode of self-administration was by intranasal inhalation, but one man self-administered all cocaine by freebasing and a second man self-administered 70% of all cocaine used by freebasing and the remaining 30% by intranasal inhalation.

During Study 1, blood plasma samples for prolactin analysis were obtained from eight patients (seven men and one woman) 24 to 72 hours after admission to the hospital, and a second plasma sample was obtained

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TABLE 1. Demographic and Cocaine Use Characteristics of 14 Men and Two Women Hospitalized for Cocaine Abuse

Subject	Sex	Age (years)	Cocaine Used	Duration of Use (years)	Method of Administration
Study 1					
1	F	30	2 g/week	4	Intranasal
2	M	38	2 g/day	2	Intranasal
3	M	24	6–8 g/week	2.5	Intranasal
4	M	27	2 g/week	3	Intranasal
5	M	27	7 g/week	3	Intranasal
6	M	36	2–4 g/week	10	Intranasal
7	M	20	1.5 g/week	2	Intranasal
8	M	43	1 g/day	4	Intranasal
Study 2					
1	F	26	3 g/day	6	60% freebase 40% intranasal
2	M	22	3 g/week	3	95% intranasal
3	M	38	3 g/day	10	70% freebase 30% intranasal
4	M	34	2–3 g/day	4	99% intranasal
5	M	38	3–4 g/day	1	Intranasal
6	M	40	1–2 g/day	2	Intranasal
7	M	28	2–5 g/day	6	Intranasal
8	M	31	5–7 g/day	4	Freebase

from them immediately before discharge from the hospital (average duration of hospitalization was 4 weeks). For study 2, carried out with seven men and one woman who were admitted to the hospital for chronic cocaine abuse, blood plasma samples were obtained 24 to 72 hours after admission to the hospital and on four subsequent occasions at weekly intervals until discharge. All patients had normal physical examinations and blood hemogram and blood chemistry values. None of the patients received any drugs or medications during their hospital stay.

Plasma samples were collected between 8 a.m. and 9 a.m. after the patients followed overnight fasting conditions and were frozen (−70 °C) before analysis for prolactin, luteinizing hormone (LH), cortisol, and testosterone (for men). Plasma LH and prolactin levels were measured in duplicate by a double-antibody radioimmunoassay procedure similar to that described by Midgley (9). Antisera and reference preparations (LER-907 for LH, hPRL-RP-1 for prolactin) were provided by the National Hormone and Pituitary Program (University of Maryland School of Medicine), supported by the National Institute of Diabetes, Digestive, and Kidney Disease, the Center for Population Research of the National Institute of Child Health, and the Agricultural Research Service of the U.S. Department of Agriculture. ^{125}I-labeled human LH and prolactin were purchased from Cambridge Medical Diagnostics (Billerica, Mass.). Results are expressed in terms of the reference preparations. Assay sensitivities were 4.4 and 4.6 ng/ml for the LH and prolactin assays, respectively; intra- and interassay coefficients of variation were 7.6% and 9.0% for the LH assay and 4.1% and 11.1% for the prolactin assay. Plasma cortisol concentrations were measured in duplicate by a direct coated tube radioimmunoassay method with a kit purchased from Clinical Assays (Cambridge, Mass.) that did not require solvent extraction. Results are expressed in micrograms per deciliter. Assay sensitivity was 2 μg/dl; intra- and interassay coefficients of variation were 4.3% and 6.5%, respectively. Plasma testosterone concentrations were measured in duplicate by a direct double-antibody radioimmunoassay method with a kit purchased from Radioassay Systems Laboratories (Carson, Calif.) that did not require solvent extraction. Results are expressed in nanograms per deciliter. Assay sensitivity for testosterone was 10.0 ng/dl; intra- and interassay coefficients of variance were 5.8% and 13.7%, respectively. All samples from the same subject were analyzed in the same assay.

TABLE 2. Prolactin Levels in 14 Men Hospitalized for Cocaine Abuse

Subject	Prolactin Level (ng/ml)	
	Admission[a]	Discharge[b]
6 (study 2)	43.9	35.4
7 (study 1)	42.9	35.0
3 (study 2)	38.4	18.8
8 (study 2)	36.9	34.7
5 (study 1)	31.9	11.3
3 (study 1)	30.5	54.4
7 (study 2)	28.9	33.6
5 (study 2)	22.1	25.3
2 (study 2)	22.0	34.0
6 (study 1)	20.6	18.8
8 (study 1)	20.3	31.7
2 (study 1)	19.6	22.6
4 (study 1)	15.4	29.0
4 (study 2)	12.0	17.3

[a]Mean±SD=27.5±10.2 ng/ml.
[b]Mean±SD=28.7±10.8 ng/ml.

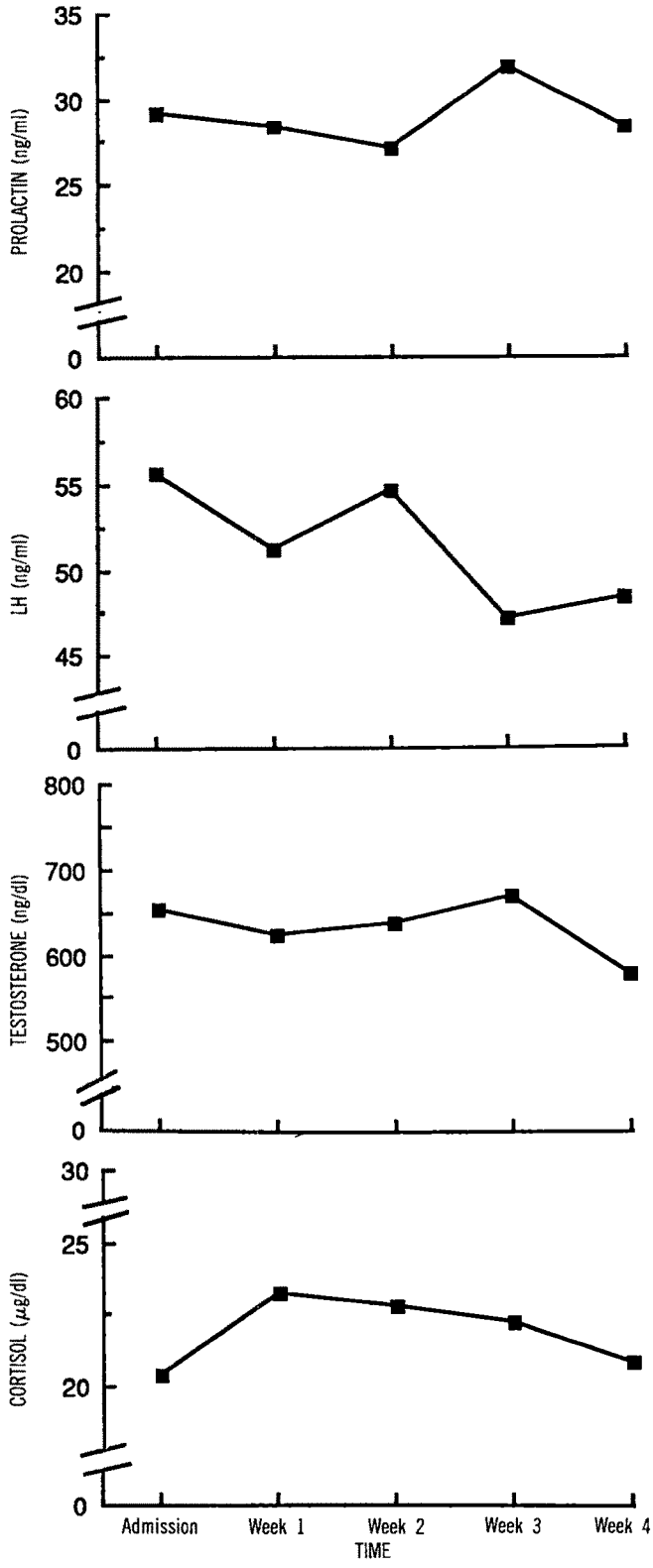
RESULTS

The plasma prolactin levels for the 14 male patients at admission and before discharge are shown in table 2. At admission, nine of the 14 men had plasma prolactin levels in the hyperprolactinemic range (>21 ng/ml), and three had plasma prolactin levels in the borderline abnormal range (19.6, 20.3, and 20.6 ng/ml). Only two patients had plasma prolactin levels that were in the normal range for adult males (15.4 and 12.0 ng/ml). Plasma prolactin levels before discharge from the hospital were higher than at admission for eight of the 14 men; seven of these eight patients had prolactin levels in the hyperprolactinemic range. Three patients (patient 7 in study 1 and patients 6 and 8 in study 2) with hyperprolactinemia at admission showed a decrease in prolactin levels before discharge, but their prolactin levels were still within the hyperprolactinemic range at this time. The mean±SD prolactin levels for all patients at time of discharge were not statistically significantly different from mean prolactin levels at time of admission. Both admission (27.5±10.2 ng/ml) and discharge (28.7±10.8 ng/ml, mean±SD prolactin levels were in the hyperprolactinemic

range. We have previously determined plasma prolactin levels in 54 normal subjects whose ages were similar to the patients who participated in this study; their mean±SD plasma prolactin level was 7.68±3.33 ng/ml.

Figure 1 shows mean prolactin, LH, testosterone, and cortisol levels for the seven men who were studied at admission and once each week for 4 weeks during treatment. Their mean prolactin levels were in the hyperprolactinemic range (>25 ng/ml). There was no significant change in mean plasma prolactin levels during the 4-week course of hospitalization as determined by repeated measures analysis of variance ($F=0.776$, $df=4, 24$, $p=0.5519$). One woman at admission to the hospital had a plasma prolactin level of 25.3 ng/ml, which increased to 50.9 ng/ml after 4 weeks. The other woman had a plasma prolactin level of 62.9 ng/ml at admission, which decreased to 35.0 ng/ml after 4 weeks of hospitalization. The mean plasma LH levels at admission were within the normal range for healthy adult men and ranged between 50 and 60 ng/ml. Plasma testosterone levels ranged from 600 to 700 ng/dl and were within the range of normal levels for healthy adult men. The mean morning plasma cortisol levels ranged between 20 and 23 μg/dl and were in the high normal range for healthy adult men (10).

FIGURE 1. Mean Prolactin, LH, Testosterone, and Cortisol Levels for Seven Male Cocaine Abusers at Admission to Hospital and During 4 Consecutive Weeks of Hospitalization



DISCUSSION

Dackis and Gold (8) have postulated that chronic cocaine abuse may result in a "decreased functional dopaminergic tone" after cocaine abstinence, and the data obtained in this study are consistent with their hypothesis. Our data, and those of Dackis and Gold (8), were obtained from patients during a period of hospitalization when routine drug testing of urine revealed that patients were not surreptitiously using cocaine or other drugs. In contrast, Gawin and Kleber (7) found a decrease in plasma prolactin levels in patients who abused cocaine; their study was carried out in an outpatient clinic when patients may have self-administered cocaine shortly before their visits to the hospital. Thus, initial suppression of plasma prolactin levels may occur after acute cocaine self-administration and be followed by an increase in plasma prolactin levels during cocaine abstinence.

There is considerable evidence that control of prolactin secretion is mediated, in part, by dopaminergic inhibitory regulation (11). It is also well known that cocaine blocks reuptake of dopamine at neural receptor sites (12–18). Recent studies (19) have shown that the cocaine binding sites associated with dopamine uptake may also be the receptors which mediate the reinforcing properties of cocaine.

Chronic cocaine administration may induce long-term derangements in neural and peripheral dopaminergic regulatory systems (20, 21). Recent studies with rats revealed that one injection of cocaine produces a long-lasting increase in tritiated dopamine release (22). Thus, persistent elevation of prolactin levels after co-

caine withdrawal may be a biological marker for a protracted cocaine abstinence syndrome. Many patients report a long-term desire to reinitiate cocaine use after protracted abstinence, and a cocaine-induced derangement in dopaminergic function may be one important factor that enhances risk for recrudescence of cocaine abuse. This hypothesis is consistent with experimental animal data which have shown that dopaminergic systems in the brain are important modulators of cocaine self-administration (23) and that dopamine agonists can substitute for cocaine in maintaining cocaine self-administration (24). There have also been preliminary reports (25) that administration of bromocriptine, a dopamine agonist, to cocaine-dependent persons induces a significant remission of drug craving and that bromocriptine may be a useful pharmacological adjunct in the treatment of cocaine withdrawal.

Is it possible that hyperprolactinemia observed in our patients hospitalized for cocaine abuse might be due to nonspecific stress factors? This hypothesis does not seem to be tenable for a number of reasons. Most stressors that induce elevations of prolactin levels in humans are associated with major physiologic manipulations, such as surgery (26). Rose (27) reported that prolactin levels increased "during parachute jumping, during motion sickness and following examinations," but he emphasized that increases in prolactin levels require "a more intense stimulus than those leading to increases in cortisol or catacholamine levels." Martin and Reichlin (28) noted that "the effects of psychologic stress on prolactin release have been systematically tested. In a few studies one of the most surprising (and negative) studies utilized as a stimulus exposure to a phobic object. Despite induction of severe anxiety the experimental subjects showed no change in blood PRL levels. This finding underlines the specificity of emotional factors inducing PRL release. Prolactin levels and prolactin responses to phenothiazines are normal in schizophrenic patients [(29)]." During previous studies, we did not observe any stress-related increment in prolactin levels as a consequence of venipuncture or intravenous catheterization for continuous blood plasma sampling (30).

Plasma LH, cortisol, and testosterone levels were within normal ranges for each subject during the course of hospitalization when hyperprolactinemia was observed. This observation suggests that chronic cocaine abuse does not produce alterations in the hypothalamic-pituitary-adrenal axis and hypothalamic-pituitary-gonadal axis that can be detected by determination of anterior pituitary, adrenal, and gonadal hormone levels as measured in this study; however, since cocaine has a relatively short duration of pharmacological action, our data do not provide information about the acute effects of cocaine on the secretory activity of these hormones. Studies designed to determine the effects of acute cocaine administration, under controlled conditions, on neuroendocrine function should be carried out.

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Bedside Differentiation of Depressive Pseudodementia From Dementia

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The authors analyzed the pretreatment clinical presentations of 14 patients with depressive pseudodementia and 28 patients with primary degenerative dementia as measured by the Mini-Mental State, the Blessed Dementia Rating Scale, and the Hamilton Rating Scale for Depression. They found that patients with pseudodementia showed significantly greater pretreatment early morning awakening, higher ratings of psychological anxiety, and more severe impairment of libido. Patients with dementia, however, showed significantly more disorientation to time, greater difficulty finding their way about familiar streets or indoors, and more impairment with dressing. The authors suggest that these findings be considered preliminary.

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Elderly patients with mixed symptoms of depression and dementia present complex diagnostic, therapeutic, and prognostic challenges. Reviews by Caine (1), Rabins (2), and McAllister (3), as well as a computerized literature search (MEDLINE and PsychINFO), yielded more than 140 articles focusing on the coexistence of depression and dementia, but few of these were empirical studies. Published data (4–10) indicate that 10% to 20% of depressed elderly patients have substantial cognitive deficits (depressive pseudodementia) and that 3% to 25% of patients with dementia of the Alzheimer type develop depressive symptoms. The most salient clinical issue is to prospectively distinguish these two groups of patients; the only current confirmatory test of depressive pseudodementia is affective and cognitive improvement with adequate antidepressant therapy and the absence of progressive cognitive loss on follow-up (1, 11–13).

Given the potentially tragic implications of misdiagnosis as well as the time involved in conducting a trial of adequate treatment, the need for valid pretreatment indicators for use by clinicians is obvious. Therefore, in this report we will offer an analysis of the utility of bedside data for distinguishing patients with depressive pseudodementia from those having primary degenerative dementia with depressive features.

METHOD

As part of a larger program of research in sleep and aging (14, 15), we have accumulated treatment response data and longitudinal information about the clinical course of patients with mixed clinical presentations, allowing us to classify them as having either depressive pseudodementia or primary degenerative dementia with depressive features.

Patients were required to meet Research Diagnostic Criteria (RDC) (16) according to the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (17) for current major depressive disorder (unipolar nondelusional) or *DSM-III* criteria for primary degenerative dementia with depressive features. Fourteen of the patients met the criteria for major depressive disorder (our pseudodementia group) and 28 met the criteria for primary degenerative dementia. All patients consented to participation in the study after its nature had been explained to them.

In addition to RDC and *DSM-III* diagnoses, the following variables were considered in assigning patients to the pseudodementia or dementia groups: previous history of affective episodes, order of appearance of symptoms, duration and progression of symptoms, response to antidepressant treatment, and subsequent clinical course. No single clinical feature was considered pathognomonic for either patient group. However, a diagnosis of depressive pseudodementia was favored in patients with previous depressive episodes, rapid onset and progression of symptoms, mood improvement with antidepressant treatment, and improvement in cognitive deficits that paralleled mood

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improvement. On the other hand, dementia with depressive features was diagnosed in patients with no previous history of affective disorder, insidious onset and gradual progression of symptoms, no improvement in cognition during antidepressant treatment despite mood improvement, and stability or actual deterioration of cognitive status at follow-up. Although the final decision regarding diagnosis was made by the principal investigator (C.F.R.), the reliability of diagnosis in a subgroup of 28 patients was assessed by a second, independent psychiatrist (D.J.B.), who assigned patients to one of the two groups according to pretreatment and follow-up global clinical ratings. Interrater agreement was 92.3% (kappa=0.82, $p<0.001$), indicating high reliability in assigning patients to subgroups.

The severity of pretreatment symptoms was rated by using the Mini-Mental State (13), the Blessed Dementia Rating Scale (18), and the Hamilton Rating Scale for Depression (19). These instruments were selected because of their widespread use in psychiatric research and ease of use in clinical practice. The Mini-Mental State, an 11-item measure with a range of 0 (severe impairment) to 30 (no impairment), assesses orientation to time and place, registration and recall of newly learned information, language, and constructional praxis. The Hamilton depression scale provides a quantitative assessment of the severity of depressive symptoms, with higher scores indicating greater severity. The first 17 items of the scale (single rater) were used. The Blessed Dementia Rating Scale is a 22-item quantitative measure of intellectual and personality deterioration based on the subject's ability to perform activities of daily living. It is scored from 0 (no impairment) to 28 (marginal impairment).

After a 14–21-day medication-free period, during which pretreatment ratings and diagnostic procedures were carried out, all 42 patients began active, open treatment with either nortriptyline or ECT (14). Each patient had a trial of nortriptyline for at least 4 weeks at adequate blood levels (50–150 ng/ml) or at least six ECTs. Following hospitalization, ratings were repeated every 6 months on the Mini-Mental State, the Hamilton depression scale, and the Blessed scale. Ratings were performed by a research nurse blind to baseline diagnostic assessment and were based on interviews with patients, family members, and primary caregivers. All patients were followed for 6–24 months; the median follow-up period was 12 months.

Sample descriptors and severity ratings for pseudodemented and demented patients were compared by using group t tests. The mean scores for each item of the Mini-Mental State, the Blessed scale, and the Hamilton scale were also compared by using group t tests. To control for type I error, we used both a Bonferroni adjustment and a multivariate analysis of variance (MANOVA).

We wished to determine the prognostic utility of global scores and individual items that showed large pretreatment group differences. As a preliminary and exploratory test of predictive validity, we performed two discriminant function analyses, the first using global test scores and the second using individual item scores with large pretreatment differences between pseudodemented and demented patients. The resulting classification accuracy was determined by comparing the predicted group membership with the actual clinical classification based on treatment response and follow-up data.

To develop an item-based discriminant function, we selected one item from the Mini-Mental State (orientation to time), three from the Hamilton scale (delayed insomnia, psychological anxiety, and loss of libido), and three from the Blessed scale (inability to find way about familiar streets, difficulty with dressing, and inability to find way about indoors). A MANOVA on these seven items revealed a significant Mahalanobis D-square statistic (19.31, $p<0.001$), thus verifying that these two populations differ reliably with respect to these items. In the discriminant function analyses, we used a jackknifing procedure (20) to verify the stability of the models. Multicolinearity was kept to a minimum in selection of the items by reviewing the correlation matrix. (The discriminant function equations and correlation matrix are available from C.F.R. on request.)

RESULTS

Pseudodemented patients achieved better global scores than demented patients on the Mini-Mental State (see table 1), as well as better scores on items assessing orientation to time ($t=4.72$, $df=40$, $p<0.001$) and place ($t=2.52$, $df=40$, $p<0.02$), on registration ($t=2.07$, $df=40$, $p<0.05$), on performance of calculations ($t=2.56$, $df=40$, $p<0.02$), on naming ($t=2.42$, $df=40$, $p<0.05$), on reading ($t=2.71$, $df=40$, $p<0.02$), on writing ($t=2.35$, $df=40$, $p<0.05$), and on copying ($t=2.01$, $df=40$, $p<0.05$). The groups did not differ on measures of short-term recall, repetition, and completing a three-stage command.

Pseudodemented patients were also less impaired than demented patients according to Blessed scale global scores (see table 1). Demented patients showed greater impairment in spatial orientation and activities of daily living, as evidenced by inability to find their way about indoors ($t=4.42$, $df=40$, $p<0.001$), inability to find their way about familiar streets ($t=4.99$, $df=40$, $p<0.001$), and difficulty with dressing ($t=4.63$, $df=40$, $p<0.001$).

By contrast, pseudodemented patients were more depressed according to Hamilton scale scores than demented patients (see table 1). Pseudodemented patients had more severe delayed insomnia ($t=2.23$, $df=40$, $p<0.05$), psychological anxiety ($t=2.60$, $df=40$, $p<0.02$), somatic anxiety ($t=2.37$, $df=40$, $p<0.05$), and loss of libido ($t=2.50$, $df=40$, $p<0.02$).

To summarize, pseudodemented patients had pretreatment ratings indicative of worse depressive symp-

TABLE 1. Characteristics and Test Scores of Patients With Depressive Pseudodementia or Dementia

Item	Patients With Depressive Pseudodementia (N=14)	Patients With Dementia (N=28)	t (df=40)	p
Hospital status			0.34	n.s.
Inpatient	11	24		
Outpatient	3	4		
Age (years)			−1.78	n.s.
Mean	75.1	71.4		
SD	5.6	8.0		
Range	66–84	50–81		
Sex			0.08[a]	n.s.
Men	3	5		
Women	11	23		
Race			1.05[a]	n.s.
White	14	26		
Black	0	2		
Education (years)			0.31	n.s.
Mean	10.1	10.5		
SD	3.0	3.4		
Age at onset of cognitive impairment (years)			−2.15	<0.05
Mean	72.8	65.7		
SD	6.3	15.0		
Age at onset of depression (years)			−0.29	n.s.
Mean	60.4	58.5		
SD	18.3	20.2		
Duration of illness (months)				
Mean	24.2	26.1		
SD	32.6	18.8		
Median	12.0	24.5	−1.25	n.s.
Range	1–120	1–72		
Blessed Dementia Rating Scale score			3.57	<0.001
Mean	7.1	10.8		
SD	2.4	3.5		
Hamilton Rating Scale for Depression score			−2.98	<0.005
Mean	20.3	15.6		
SD	4.8	4.8		
Mini-Mental State score			−4.31	<0.001
Mean	23.4	17.1		
SD	2.9	6.6		

[a]This is a chi-square value (df=1) rather than a t value.

toms but better cognitive capacity and capacity for activities of daily living than demented patients. Global rating scale scores differed between groups at the 0.001 level (Mini-Mental State and Blessed scale) and the 0.005 level (Hamilton scale). Although after Bonferroni correction only two of 50 items (the Mini-Mental State item orientation to time and the Blessed scale item difficulty with dressing) remained significant, a MANOVA on the seven individual items selected for the preliminary test of predictive validity was highly significant (see table 2).

We asked whether these pretreatment differences in global ratings of cognitive and affective impairment have prognostic utility. That is, do they predict which patients will have a clinical course consistent with affective disorder and which will show progressive dementia? As a preliminary test of predictive validity, we entered total Mini-Mental State, Hamilton scale, and Blessed scale scores into a forced discriminant function analysis. The resultant discriminant function correctly predicted actual group membership, determined by follow-up data, in 33 (78.6%) of 42 cases (kappa=0.56, p<0.001). Two (14.3%) of 14 pseudodemented patients were misclassified as demented, and seven

TABLE 2. Discriminant Function Analysis Items That Correctly Classified 38 of 42 Patients With Depressive Pseudodementia or Dementia[a]

Item and Scale	Partial F Ratio (df=1, 34)	p
Orientation to time (Mini-Mental State)	11.40	0.002
Psychological anxiety (Hamilton Rating Scale for Depression)	10.30	0.003
Inability to find one's way about familiar streets (Blessed Dementia Rating Scale)	9.10	0.005
Difficulty with dressing (Blessed scale)	3.50	0.07
Delayed insomnia (Hamilton scale)	1.30	n.s.
Loss of libido (Hamilton scale)	1.20	n.s.
Inability to find one's way about indoors (Blessed scale)	0.04	n.s.

[a]90.5% of the patients were correctly classified by using these items. When the first four items were retained by using backward elimination, 85.7% of the patients were correctly identified. The last three items were not strong predictors and accounted for a small portion of the variance.

(25%) of 28 demented patients were misclassified as pseudodemented.

We next addressed the prognostic utility of pretreatment differences in individual item ratings of cognitive and affective impairment. A forced discriminant function using seven individual items (see table 2) correctly classified 38 (90.5%) of the 42 patients (kappa=0.79, $p<0.001$): 13 (92.9%) of the 14 pseudodemented patients and 25 (89.3%) of the 28 demented patients. The Mini-Mental State item orientation to time was the most highly weighted predictor variable, followed by the Hamilton scale item psychological anxiety and the Blessed scale item inability to find one's way about familiar streets.

DISCUSSION

These preliminary findings suggest that pretreatment bedside ratings of affective and cognitive impairment are statistically and clinically reliable in distinguishing depressive pseudodementia from primary degenerative dementia with depressive features. Thus, as reflected by the kappa of 0.56, use of global ratings as predictors resulted in modest levels of agreement (78.6%) between observed and predicted group membership. A classification function using individual items from three scales (from the Mini-Mental State: orientation to time; from the Blessed scale: inability to find one's way about familiar streets, inability to find one's way about indoors, and difficulty with dressing; from the Hamilton scale: delayed insomnia, psychological anxiety, and loss of libido) correctly predicted pseudodementia versus dementia in 90.5% of patients. This result must be regarded as preliminary, however, until the discriminant function is tested and cross-validated in an independent sample of patients.

Empirical studies such as this are relatively few, and to our knowledge none has used a multivariate statistical approach. Indeed, such an approach has not been feasible in most studies because sample size requirements were not met. For instance, in his 1983 review of this area, McAllister (3) reported a total of 25 patients with depressive pseudodementia; their mean age was 60.5 (range=22–85). We will now briefly review the major findings from the published empirical studies in relation to the current observations of differences in cognition, neurovegetative symptoms, and implications for treatment.

Cognition

Previous studies of the clinical phenomenology of coexistent depression and dementia include reports by Folstein et al. (6, 13), Rabins et al. (21), and Reynolds et al. (15). In 1975 (13) and 1979 (6), Folstein et al. reported that patients with depressive pseudodementia frequently scored around 22 or 23 on the Mini-Mental State, whereas those with established dementia typically scored less than 22. Similarly, in a 1984 study of depressed elderly patients with cognitive impairment, Rabins et al. (21) suggested that depressive pseudodementia is distinguished by a high frequency of previous depression, current depressed mood, delusions, and higher Mini-Mental State scores than found in demented control subjects. Our current findings of higher Mini-Mental State scores and higher Hamilton scale depression ratings in pseudodemented than in demented patients confirm through systematic follow-up the previous work of Folstein et al. and Rabins et al.

Raskin and Gershon (22), in a 1980 study of elderly patients with mixed clinical presentations, reported that depressed demented patients showed particular difficulties in attending to and concentrating on the Mini-Mental State. Our demented group showed the same pattern of dysfunction. Conversely, as noted in Caine's 1981 review (1), patients with a depression-related "subcortical" dementia should show relative preservation of the ability to learn new material, in contrast to patients with "cortical" dementia (e.g., Alzheimer's dementia). Our pseudodemented patients did in fact show superior attention and registration than did our demented patients but did not demonstrate statistically better recall. As predicted by Caine's model, the pseudodemented group outperformed the demented group on such other "cortical" functions as naming, reading, writing, calculation, and copying. Similarly, the scores on the Blessed scale items indicating greater spatial disorientation and dressing apraxia in our demented group appear to be consistent with Caine's model.

In his 1979 review, Wells (12) emphasized rapid progression of symptoms in pseudodementia as well as complaints of cognitive loss and frequent "I don't know" responses, contrasted with a slower progression of symptoms and more "near-miss" answers in dementia. Our pseudodemented patients had a significantly later age at onset of cognitive impairment than did the demented group (72 versus 65 years) and also had a shorter median duration of cognitive symptoms, consistent with Wells's observation.

Neurovegetative Symptoms

Lazarus et al. (23), investigating depressive symptoms in demented patients, noted significantly higher scores on items assessing intrapsychic rather than neurovegetative symptoms of depression (e.g., anxiety and feelings of helplessness, hopelessness, and worthlessness). Our current observation that pseudodemented patients differ from demented patients by having more severe disturbance in items measuring "vital" functions (e.g., sleep and libido) is consistent with the pattern of differences reported by Lazarus et al.

In a 1987 report based on 57 outpatients with Alzheimer's disease, Reisberg et al. (24) found that 58% had substantial behavioral symptoms, including diurnal rhythm disturbance. In our current study, we found more severe early morning awakening in the pseudodemented group than in the demented patients,

an observation consistent with sleep physiological data in this area (25). However, it is known that as dementia progresses there is a breakdown or loss of consolidation in sleep and wakefulness, as evidenced by nocturnal wandering and daytime sleepiness, a pattern quite distinct from the early morning awakening of late-life depressive patients (25, 26).

CONCLUSIONS

To date, there is no consensus among empirical studies on the issue of whether coexisting cognitive impairment and major depression are usually precursory to a progressive dementing illness. For example, Reifler et al. (9), in a 1982 study of 88 patients with cognitive impairment and depression, noted that only 15% seemed to have cognitive impairment due to depression and that combined dementia and depression was far more common than depressive pseudodementia. Similarly, in an 8-year follow-up study of 22 patients with depressive "pseudodementia," Kral (27) reported that 20 patients had become permanently demented on follow-up. By contrast, in the previously mentioned study by Rabins et al. (21), coexisting depression and cognitive impairment did not usually presage a progressive dementia. In our treatment study (14), a minority (37.5%) of patients with mixed symptoms showed clinically significant improvement in cognitive function with adequate treatment of depression. In a separate naturalistic follow-up study (15), we observed that favorable outcome at 2 years was associated with initially greater depressive symptoms (Hamilton scale depression score of 21 or more), higher cognitive function (Mini-Mental State score more than 21), and neurovegetative changes of depression, such as early morning awakening (i.e., sleep efficiency less than 75%). The lack of consensus in this area probably reflects variance related to sampling, diagnostic criteria, and inadequate or poorly standardized antidepressant therapy. In any case, most workers agree that a clear depressive syndrome established by operational criteria and documented quantitatively by scales such as the Hamilton scale should be recognized and appropriately treated to relieve suffering, even if subsequent deterioration is not affected.

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Lack of Efficacy of Carbamazepine in the Treatment of Panic Disorder

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The authors conducted a controlled study of carbamazepine in the treatment of 14 patients with panic disorder. Although there was a statistically significant reduction in symptoms of anxiety on several measures, only one of the patients was judged to have a marked and sustained clinical improvement while taking carbamazepine. Forty percent of the patients had a decrease in frequency of panic attacks during carbamazepine treatment, 50% had an increase, and 10% showed no change. The presence of either EEG abnormalities or prominent psychosensory symptoms did not predict response to carbamazepine. These findings are discussed within the context of an epileptiform model for panic disorder.

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Panic attacks, with their paroxysmal onset, short duration, altered state of awareness, and kaleidoscope of autonomic symptoms, have been hypothesized to arise from temporal lobe and limbic substructures (1). Several lines of indirect evidence support this hypothesis. The classic research of Penfield, Jasper, and colleagues (2) demonstrated that electrical stimulation of the temporal cortex could produce a number of emotions, including fear, in humans. Gloor et al. (3) showed that stimulation of the limbic system most commonly produces sensations of fear in awake human subjects. Patients with partial complex seizures of temporal lobe origin may manifest ictal fear as part of their seizures (4, 5), although this may be an uncommon occurrence (6). Procaine hydrochloride, an activator of the limbic system, has been shown to occasionally induce episodes of extreme fear or panic in human subjects (7). Of interest also, an abnormal hemispheric asymmetry of parahippocampal flow in panic disorder was recently identified by means of positron emission tomography (8).

Although the vast majority of patients with panic disorder have normal EEGs (9, 10), these patients frequently exhibit a high degree of psychosensory phenomena akin to those experienced by patients with temporal lobe epilepsy (9). Thus, acceptance of the apparent lack of EEG abnormalities must be tempered by the failure of surface EEG studies to detect abnormal activity in deeper brain areas such as the limbic system (11). Moreover, some patients with panic attacks do show concomitant evidence of a seizure disorder and may improve with anticonvulsant therapy (12). In fact, a subgroup of patients with "atypical" symptoms has been reported to display abnormal EEG findings (13). Finally, a preliminary report on the use of brain electrical activity mapping in panic disorder supports a role for temporoparietal abnormalities in this disorder (14).

Even though the differentiation of panic disorder from partial complex seizures does not pose much of a dilemma on clinical grounds alone (15), these observations underscore the theoretical impetus for exploring a hypothetical link between panic disorder and temporal lobe and limbic dysfunction, including, but not exclusively limited to, possible epileptiform activity. Recent experience with the potent benzodiazepine anticonvulsant clonazepam suggests that it is an effective antipanic agent (16, 17). There is, therefore, an ample rationale for exploring the efficacy of other anticonvulsants in the treatment of panic disorder.

Carbamazepine, a tricyclic anticonvulsant, has been proven effective in the treatment of complex partial seizures of temporal lobe origin (18). It has also been shown to be effective in the treatment of affective disorders (19, 20), which themselves share many features with panic disorder (21). In this article we report the results of a controlled study of carbamazepine in the treatment of panic disorder.

METHOD

Eighteen patients who met the Research Diagnostic Criteria (22) for panic disorder and/or the *DSM-III* criteria for panic disorder or agoraphobia with panic attacks entered the study after giving their written informed consent. All patients were judged to be free of medical illness after a complete physical examination, SMA-12, CBC, thyroid function tests, ECG, and chest

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X-ray. Seventeen of the 18 patients received EEGs. Of this group, eight patients had recordings with nasopharyngeal leads, including four patients who, in addition to nasopharyngeal techniques, were also examined after sleep deprivation. Of the 17 patients evaluated with EEGs, 15 had EEGs that were interpreted as totally normal. One patient was found to have low-voltage irregular background activity on routine testing, and one patient had nonspecific slowing with the nasopharyngeal leads. None of the patients demonstrated focal epileptiform activity. Eleven women and seven men (mean±SD age=31.4±5.6 years) initially agreed to participate in the study; they had been ill a mean±SD of 7.6±5.9 years before entering the clinical trial.

All patients had a placebo period of at least 2 weeks before starting carbamazepine. Carbamazepine, in pink capsules which were identical to those for placebo, was administered blindly to patients. Research psychiatrists (M.S. and T.U.), who were not blind to the patients' medication status, prescribed carbamazepine with the goal of achieving a therapeutic response at a maximally tolerated dose, not to exceed 1800 mg/day in four divided doses. Although the research psychiatrist was given optimal flexibility in the rate of dosage increase, patients were generally started on a dose of 200 mg/day. Doses were increased at the rate of 200–600 mg/week. Therapeutic effects were weighed against side effects and, in most cases, serum blood levels; hence, the maximum doses and the duration of the trials were different for each of the patients. Overall, the mean±SD duration of treatment with carbamazepine was 66.0±43.4 days (range=22–188 days). The mean±SD peak dose of carbamazepine was 679±299 mg/day (range=200–1200 mg/day); the median dose was 800 mg/day. The mean carbamazepine blood level at peak dose was 8.4±1.6 μg/ml (range =5.9–10.6 μg/ml).

Global improvement ratings (0=worse or no change, 1=minimal improvement, and 2=moderate to marked improvement), made by the treating physicians, were ascertained by thorough chart review of all patients who completed at least a 3-week trial of carbamazepine (N=14). These global ratings were subject to obvious potential bias, since they were based on the impressions of nonblind physicians who were treating the patients.

For a subgroup of patients (N=10), more detailed assessments of change were obtained by the use of objective rating scales. For example, the patients in this smaller sample completed weekly self-ratings on the State-Trait Anxiety Inventory, state form (23), and the SCL-90 (24). Patients also completed an NIMH Panic Attack Inventory (available from the authors on request) immediately after each panic attack. Throughout the study, patients were evaluated weekly by a trained research nurse who, like the patients, was blind to treatment status. At each of the patient's weekly visits, a Zung Anxiety Scale (25) was completed by the research nurse. In addition, the number of panic attacks during the previous week was recorded by the research nurse after she had carefully reviewed the panic attack inventory with the patient. For the purpose of this study, the requirement that all panic attacks be experienced by the patient as "unprovoked-spontaneous" was added to the *DSM-III* criteria for panic attacks. Situational panic attacks or other episodes of anxiety that could not be clearly identified as spontaneous in nature were excluded. Thus, in this study the criteria for calculating the frequency of panic attacks were extremely rigid compared to standards typically used in other research settings or even the revised guidelines recently adopted by our own unit (26). For purposes of statistical analysis, all comparisons in this subgroup of 10 patients were between the week before initiation of carbamazepine treatment (while the patients were taking placebo) and the last week of treatment at the maximum dose of carbamazepine administered. A two-tailed paired t test or Wilcoxon's signed-ranks test was used for each of these pretreatment versus highest dose comparisons. Spearman rank-order correlations were used to examine relationships between the various outcome measures.

Psychosensory symptoms were rated before treatment by means of the Silberman-Post Psychosensory Rating Scale (27). This structured interview elicits information on the presence or absence of symptoms seen in temporal lobe epilepsy. In a previous study that used this rating scale (27), patients with temporal lobe epilepsy reported more than eight symptoms, whereas a medical control group reported fewer than two of these epileptoid symptoms. The number of psychosensory symptoms that occurred during a panic attack was recorded for each of our patients. The patients were then dichotomized as having either high or low psychosensory profiles by separating them along the median psychosensory score for the entire group. The high and low psychosensory subgroups were compared on a number of outcome measures by means of the Mann-Whitney U test, two-tailed.

All data are expressed as mean±SD, and p values greater than 0.10 are reported as nonsignificant.

RESULTS

Four of the 18 subjects dropped out of the study before completing a 3-week trial, which we felt was the minimum time necessary to allow for an assessment of drug efficacy. The reasons for stopping carbamazepine were as follows. One patient became too "activated" while taking carbamazepine, one patient developed dizziness and blurred vision, and one patient developed a pruritic rash. The fourth patient showed a dramatic positive response to carbamazepine but demanded that she be treated on an open basis. Since this patient's very rapid improvement might have represented a placebo response, her data were not included in the statistical analysis. Thus, 14 of the 18 subjects

TABLE 1. Behavioral Ratings of 10 Panic Patients When Taking Placebo and Carbamazepine

Measure	Score: Placebo Mean	Placebo SD	Carbamazepine Mean	Carbamazepine SD	Change Mean	Change SD	t (df = 9)	p
State-Trait Anxiety Inventory, state form	60.6	10.1	59.0	11.1	−1.6	4.9	−1.04	n.s.
Zung Anxiety Scale	57.1	13.8	52.6	12.6	−4.5	4.9	−2.91	0.02
SCL-90								
Global severity index	1.5	0.8	1.4	0.8	−0.1	0.4	−0.84	n.s.
Phobic anxiety subscale	2.0	1.4	1.7	1.1	−0.3	0.6	−1.51	n.s.
Generalized anxiety subscale	2.2	1.0	1.6	0.9	−0.5	0.8	−2.22	0.05
Panic anxiety subscale	1.6	1.0	1.5	1.0	−0.1	0.6	−0.61	n.s.
Depression subscale	1.8	1.0	1.8	1.2	−0.0	0.6	−0.00	n.s.

(78%) completed at least a 3-week trial of carbamazepine under blind conditions.

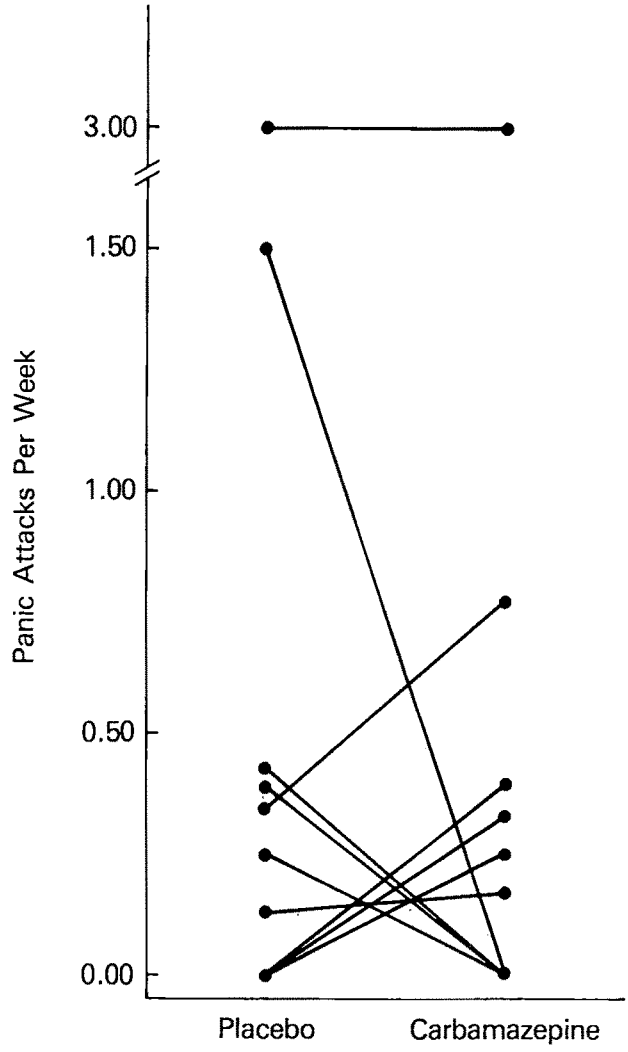
The nonblind physicians' global ratings of their patients during treatment with carbamazepine yielded unimpressive results: only one patient (7%) was thought to have shown moderate to marked improvement while taking carbamazepine, nine patients (64%) showed a minimal degree of improvement, and four patients (29%) showed no change or some worsening.

Behavioral rating measures before and during carbamazepine treatment are summarized in table 1 for the subgroup of 10 patients who received the detailed and objective evaluations during the study. Again, there were no significant changes in the State-Trait Anxiety Inventory scores or in any of the SCL-90 subscale scores except for those on the generalized anxiety subscale. There was a clinically unimpressive but statistically significant drop in the Zung Anxiety Scale scores while patients were taking carbamazepine.

Figure 1 illustrates the number of panic attacks per week experienced by the 10 patients before (while taking placebo) and during carbamazepine treatment. Four patients (40%) had a complete cessation of panic attacks, five (50%) experienced an increase, and one (10%) showed no change. Overall, there was no significant change in the number of panic attacks from before to during carbamazepine treatment (Wilcoxon's signed-ranks test).

There were strong positive correlations between the State-Trait Anxiety Inventory and Zung anxiety ratings while the patients were taking placebo ($r=0.80$, $df=8$, $p<0.01$) and between those ratings while they were taking carbamazepine ($r=0.83$, $df=8$, $p<0.005$). There was a positive correlation between carbamazepine dose and carbamazepine blood level ($r=0.60$, $df=9$, $p<0.05$). There were no significant correlations between carbamazepine dose and changes in state anxiety score, Zung anxiety score, any SCL-90 subscale score, or number of panic attacks. There was a significant correlation between carbamazepine blood level and change in the Zung anxiety score ($r=-0.72$, $df=6$, $p<0.05$), indicating that patients with higher blood levels showed greater improvement in their Zung anxiety scores. Carbamazepine blood level did not, however, significantly correlate with any other outcome measure.

FIGURE 1. Frequency of "Spontaneous" Panic Attacks in 10 Panic Patients When Taking Placebo and Carbamazepine



The mean number of psychosensory symptoms acknowledged by patients on the Silberman-Post Psychosensory Rating Scale was 6.9±4.5 (range=1–18). This was substantially more than the number seen in normal control subjects (mean of fewer than three symptoms) and in hypertensive medical control subjects (fewer than two symptoms) and was in a range similar to that observed in affectively ill patients (mean of more than six symptoms) and those with complex partial seizures (mean of more than eight symptoms) (27, 28).

The number of psychosensory symptoms acknowledged did not significantly correlate with any outcome measure. When patients were dichotomized as having either high (seven or more symptoms) (N=6) or low (fewer than seven symptoms) (N=5) psychosensory profiles, the two subgroups did not differ significantly on any outcome measure (Mann-Whitney U test). Presence or absence of EEG abnormalities did not distinguish carbamazepine responders from nonresponders (Fisher's exact test, two-tailed).

DISCUSSION

This is the first study, to our knowledge, to systematically examine the efficacy of carbamazepine in the treatment of panic disorder. While our preliminary experience with carbamazepine in panic disorder suggested that some patients had a modest improvement across a variety of symptoms (29), our current, more extensive findings suggest that carbamazepine has limited value in the treatment of most patients suffering from panic disorder with or without agoraphobia. On most outcome measures, patients taking carbamazepine failed to show any benefit over the preceding time period when they were taking placebo. While a small decrease in scores was noted on the Zung Anxiety Scale, this was of minimal clinical significance.

A recent report (13) described several patients who had atypical panic attacks associated with hostility, irritability, severe derealization, and social withdrawal. Most of these patients had some temporal lobe EEG abnormalities, and some responded to carbamazepine. We specifically evaluated patients for the presence of psychosensory phenomena and also documented EEG findings. As previously reported by our unit (9), we found a high prevalence of psychosensory disturbances in our patients, but 12 of the 14 patients had normal EEGs. Even for the two patients who had alterations in their EEGs, the changes were nonspecific and totally devoid of focal epileptiform activity. Moreover, we found no relationship between either of these measures of temporal lobe function and response to carbamazepine. Thus, although it would be reasonable to speculate that panic patients with evidence of epileptiform abnormalities might respond to an anticonvulsant, our findings suggest this is not true for panic patients without concomitant evidence of complex partial seizures. Interestingly, these findings parallel those seen in the treatment of affective disorders with carbamazepine, in which EEG abnormalities or epilepticlike symptoms do not predict response to carbamazepine (30). Our findings are also consistent with those of other investigators (7) who failed to find a relationship between degree of procaine-induced activation of EEG beta activity over the temporal cortex and degree of response to carbamazepine in patients with borderline personality disorder.

It should be noted that our findings of a lack of efficacy of carbamazepine in panic disorder do very little to disprove the involvement of an underlying ictal process in panic disorder. Anticonvulsants vary markedly in their ability to treat different kinds of seizures and even differentially affect seizures at various stages of their development (31). Alprazolam (32) and clonazepam (16, 17), both benzodiazepines with anticonvulsant activity, are clearly effective as antipanic agents. Therefore, carbamazepine's failure to treat panic disorder does not allow us to generalize about the role of epileptiform processes in the pathophysiology of panic disorder. As mentioned earlier, recent techniques permitting sophisticated analysis of EEG data (14) suggest that this is still an area worthy of further investigation.

The apparent differential efficacy of clonazepam and carbamazepine does, however, permit us to speculate about mechanisms involved in the mediation of pathological anxiety and its treatment. Clonazepam, which is highly effective in the treatment of panic disorder (16, 17), is active at the classical central-type benzodiazepine receptor (33), which is part of the γ-aminobutyric acid receptor/chloride ionophore macromolecular complex. In contrast, carbamazepine, which shows little antipanic activity, appears to exert its anticonvulsant effects at the so-called peripheral-type benzodiazepine receptor (33). Clonazepam's superiority in the treatment of panic attacks suggests preferential involvement of the central-type benzodiazepine receptor and associated mechanisms in the mediation of panic anxiety; the role of peripheral-type sites in anxiety requires further study.

When one moves away from carbamazepine's status as an "anticonvulsant" and looks at some of its effects on various neurotransmitter systems, its lack of efficacy in the treatment of panic disorder becomes more understandable. On the basis of two separate models of panic disorder, carbamazepine would be predicted to lack anxiolytic/antipanic activity and perhaps even to be panicogenic.

A prominent hypothesis of anxiety disorders suggests that activity of the major brain noradrenergic site, the locus ceruleus, is related to the development of anxiety or fear (34). Drugs with anxiolytic or antipanic effects, such as benzodiazepines (35, 36) or tricyclic antidepressants (37), depress locus ceruleus activity, whereas anxiogenic substances, such as yohimbine, increase locus ceruleus firing (38, 39). On the basis of this model, carbamazepine, which acutely increases the firing rate of the locus ceruleus (40), would be predicted to have anxiogenic, not anxiolytic, properties.

Another model of panic disorder has led to examination of the greater sensitivity of patients with panic disorder to caffeine (41–43). Caffeine's effects on anxiety are believed to be possibly mediated through its action as an adenosine antagonist (44). Carbamazepine has been shown to have effects similar to those of caffeine at the adenosine receptor, also acting as an adenosine antagonist (45, 46). Thus, using this model of anxiety, one would not expect carbamazepine to exhibit anxiolytic effects.

In summary, we found that carbamazepine lacked substantial clinical efficacy in the treatment of panic disorder. Although little can be concluded regarding the hypothesis that panic disorder is an epileptiform illness, further studies with other anticonvulsants should be undertaken to clarify this issue. In consideration of carbamazepine's effects on the locus ceruleus and at the adenosine receptor, our findings are consistent in showing a lack of anxiolytic or antipanic action. Still, carbamazepine may have a role to play in the management of anxiety disorders by treating atypical panic attacks such as those associated with seizure disorders (12, 13) and use of cocaine (47) or as an adjunct in facilitating withdrawal from alprazolam (48). These possibilities need further exploration.

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S-Adenosylmethionine Treatment of Depression: A Controlled Clinical Trial

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The antidepressant properties of S-*adenosylmethionine, an endogenous methyl donor, were studied in inpatients who met the* DSM-III *criteria for major depression. Nine patients given intravenous* S-*adenosylmethionine and nine given low oral doses of imipramine were compared in a double-blind design for 14 days. The* S-*adenosylmethionine produced superior results by the end of the first week of treatment. By the end of the second week, 66% of the* S-*adenosylmethionine patients had a clinically significant improvement in depressive symptoms, compared to 22% of the imipramine patients. Side effects appeared to be fewer with* S-*adenosylmethionine than with imipramine during the last 5 days of the study.*

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A wide variety of antidepressant compounds are effective in the treatment of major depression. In spite of a great diversity in structure and pharmacological properties, all of these agents usually require several weeks before a clinically significant antidepressant response is realized. This lag in antidepressant activity places the patient at risk of suicide and considerable suffering. ECT is the recommended procedure in cases where a rapid therapeutic response is mandated. However, an endogenous compound with rapid antidepressant activity would be not only a clinically useful alternative to ECT but also an important contributor to our understanding of the underlying causes of depression.

We initiated this study to confirm the reported antidepressant properties of *S*-adenosylmethionine in depressed patients requiring hospitalization.

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METHOD

Patients between the ages of 20 and 65 years who had both a *DSM-III* diagnosis of major depression and a score higher than 23 on an augmented 31-item version of the Hamilton Rating Scale for Depression were considered for inclusion in the study. The augmented 31-item Hamilton depression scale has added items tapping atypical depressive symptoms such as hyperphagia, hypersomnia, psychomotor retardation, and feelings of helplessness, hopelessness, and worthlessness. All patients who met these criteria were screened for entry into the study and were blindly rated by the investigators while they were in the hospital. In almost all instances the same person rated each patient throughout the study. Patients who had histories of major medical illness, personality disorder, or substance or alcohol abuse in the 6 months preceding the study or who refused to given written informed consent were excluded. Patients with a history of failure to respond to the equivalent of 150 mg/day or more of imipramine given for 4 weeks were also excluded to eliminate subjects with a history of resistance to tricyclic antidepressant treatment.

Twenty-two depressed inpatients were considered for inclusion in the study and treated. Eleven patients received *S*-adenosylmethionine, and 11 received low doses of imipramine. Four patients (two in each drug treatment group) did not complete the study; one was withdrawn after receiving a diagnosis of antisocial personality disorder, two refused to continue because of discomfort with the intravenous procedure, and one was withdrawn because results of a test for syphilis were positive. Thus, a total of 18 patients, nine taking *S*-adenosylmethionine and nine taking imipramine, completed the study and are included in this report.

All of the patients fulfilled the *DSM-III* criteria for major depression, and a majority (eight of nine *S*-adenosylmethionine patients and seven of nine imipramine patients) also satisfied the criteria for melancholia. Two patients in each treatment group demonstrated mood-congruent psychotic symptoms. One patient in the imipramine group and none in the *S*-adenosylmethionine group reported a past episode of mania.

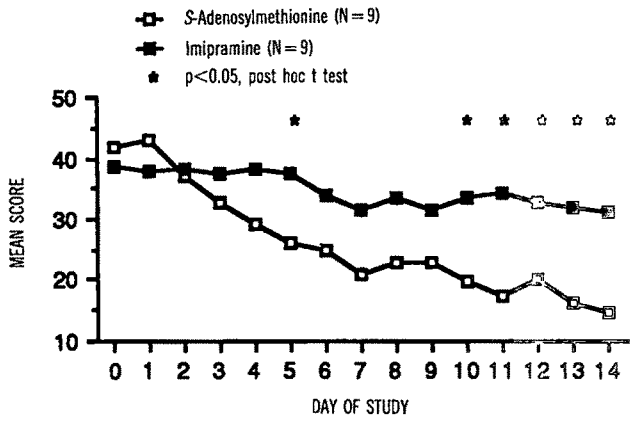
A double-blind design was used in which patients

were randomly assigned to either the *S*-adenosylmethionine (N=9) or the imipramine (N=9) treatment group. The duration of the study was 16 days: a 2-day baseline evaluation and medication washout and 14 days of drug treatment. All patients received both an intravenous infusion and capsules each day, but only one of these methods delivered active medication. The placebo and imipramine (50-mg) capsules appeared identical. Patients in the imipramine group were given imipramine titrated up to 150 mg/day in divided doses over 4 days; they then received that dose through the rest of the trial. These patients were also given intravenous saline infusions each day.

Patients in the *S*-adenosylmethionine group received placebo capsules and were given increasing doses of *S*-adenosylmethionine, from 200 mg to 400 mg/day i.v., over 3 days. They were maintained at a 400-mg/day dose throughout the rest of the study. The *S*-adenosylmethionine infusions were supplied by BioResearch, S.p.A., Milan, Italy. The infusions were prepared daily by the pharmacist using aseptic technique; 200–400 mg of *S*-adenosylmethionine were dissolved in 5 cc of sodium hypophosphate. The dissolved medication was added to 250 cc of normal saline. The solution was infused over a 20-minute period each morning starting at 10:00 a.m. The placebo and *S*-adenosylmethionine solutions had the same appearance, and the method of delivery was identical. The nursing staff, raters, and patients were blind to the type of infusion. Patients could not distinguish placebo from active infusions. The augmented Hamilton depression scale and the Somatic Symptom Checklist (David Kupfer, M.D., personal communication) were administered between 10:00 and 11:00 a.m. daily. The Beck Depression Inventory was completed by the patients at baseline and again on the last day of the study. CBC, SMA-18, urinalysis, thyroid function tests, ECG, and a dexamethasone suppression test (DST) were performed at baseline and on the last day of the study. Vital signs, including blood pressure, pulse, and respiration, were recorded at baseline evaluation and on each study day 15, 30, and 60 minutes after the infusion was started.

Categorical variables were analyzed by chi-square test or Fisher's Exact Probability Test. The total Hamilton scale, Somatic Symptom Checklist, and Beck inventory scores for the two groups at baseline were analyzed by Student's t test. For comparisons of the two medications with respect to continuous outcome variables recorded over time, a repeated measures analysis of variance (ANOVA) was used. This analysis included the main effects (treatment and study day) and their interaction (Treatment by Day). Baseline washout scores were covariates, and the within-subject degrees of freedom were adjusted by the Greenhouse-Geisser correction (1). When significant ANOVA effects were observed, the two treatments were compared by trend analysis and two-tailed t test. Comparisons of changes in individual items from baseline were analyzed by two-tailed t test. For t test comparisons the Bonferroni correction for multiple tests was used. Homogeneity of variance was assessed by Levene's test (2).

FIGURE 1. Scores on the Hamilton Depression Scale of Depressed Patients Receiving *S*-Adenosylmethionine or Imipramine[a]



[a]F=4.9, df=1, 16, p<0.04.

RESULTS

The mean±SD age of the 18 (five male and 13 female) patients who completed the study was 43±13 years. There were no significant differences between treatment groups in age, sex, positive family history of depression or alcoholism, precipitating life events, or duration of illness. About half of the patients in each group had received conventional antidepressant medication in the month preceding the study (χ^2=0.22, df=1, n.s.). The mean±SD duration of illness in the current episode was 9.5±5.7 weeks for the *S*-adenosylmethionine group and 9.6±6.4 weeks for the imipramine group (t=0.02, df=15, n.s.). At baseline washout the mean±SD 31-item Hamilton depression scores were 40.0±7.3 for the *S*-adenosylmethionine group and 39.0±7.5 for the imipramine group (t=0.29, df=16, n.s.). The 21-item Hamilton depression scale scores for these two groups were 31.4 and 30.8, respectively, indicating a marked degree of depression, which is typical of our depressed inpatient population. (The variances were homogeneous by Levene's test: F=0.32, df=1, 16, n.s.).

A two-way repeated measures ANOVA with covariance adjustment of baseline Hamilton depression scores showed a significant treatment effect (F=8.4, df=1, 14, p<0.02) and Treatment by Day interaction (F=5.60, df=13, 208, p<0.001) and remained significant when degrees of freedom for the within subject factor were reduced by the Greenhouse-Geisser correction (see figure 1).

Trend analysis with covariance adjustment of baseline scores was performed to decompose the significant Treatment by Day interaction into its orthogonal components. In the trend analysis, only the linear compo-

nent was significant; it accounted for 76.2% of the variance of the interaction. This significant trend analysis suggests that both treatment groups improved linearly over time, but at significantly different rates. No threshold effect was observed, and the less conservative t test with the Bonferroni adjustment for multiple t tests became significant at day 5 ($t=2.6$, $df=16$, $p<0.02$) and remained so from day 10 through day 14 ($t=2.4$ to 3.91, $df=16$, $p<0.05$). The mean±SD Hamilton depression scores on day 14 were 14.6±9.3 for the *S*-adenosylmethionine group and 31.2±10.6 for the low-dose imipramine group ($t=3.54$, $df=16$, $p<0.003$, with the Bonferroni correction). The efficacy of treatment with *S*-adenosylmethionine may also have been reflected in the patients' scores on the self-report measure, the Beck inventory, at washout and on day 14; there was a 45% decrease in the scores of the *S*-adenosylmethionine group and a 32% decrease in those of the imipramine group. The Beck inventory score on day 14 was significantly lower in the *S*-adenosylmethionine group compared to that of the imipramine group ($t=2.23$, $df=14$, $p<0.05$, with the Bonferroni correction).

Using the patients' percent changes from baseline to day 14 on the total Hamilton depression score, we considered a reduction of more than 50% to be a successful treatment response, 25% to 50% a partial response, and less than 25% a failure. Two-thirds (N=6) of the nine *S*-adenosylmethionine patients were treatment responders, and one-third (N=3) demonstrated a partial response, whereas more than three-quarters of the patients in the imipramine group (N=7, 78%) were nonresponders, and only two (22%) were responders. This difference in treatment response between patients taking *S*-adenosylmethionine and those taking imipramine was significant ($\chi^2=12$, $df=1$, $p<0.01$); however, the chi-square test requires that no more than 20% of the cells have a frequency of less than 5, so when the responses of partial responders and responders were combined, significance was obtained ($\chi^2=11.5$, $df=1$, $p<0.0007$; $p=0.0023$ by Fisher's exact test).

There were three subjects in the imipramine group and six in the *S*-adenosylmethionine group who were nonsuppressors on the DST. Nonsuppression on the DST was not related to treatment outcome ($p=0.637$ by Fisher's exact test). Having taken or not taken antidepressant medication before the trial and duration of illness were not related to treatment outcome ($p=0.637$ and $p=0.188$, respectively, by Fisher's exact test).

Between-group comparison of scores for individual items on the Hamilton depression scale on day 14 demonstrated a significantly greater improvement for *S*-adenosylmethionine patients than imipramine patients on items concerning suicide, initial insomnia, delayed insomnia, anhedonia, psychic anxiety, helplessness, worthlessness, and hypersomnia (see table 1). The core depression score (3, 4) (composed of Hamilton scale items for depression, guilt, suicide, insomnia, anhedonia, psychic anxiety, and anergia) was improved by 74% in the *S*-adenosylmethionine group, compared to 29% in the imipramine group. The day 14 core depression score for the *S*-adenosylmethionine group was 4.4, compared to 12.9 for the imipramine group ($t=4.65$, $df=16$, $p<0.001$). The two patients in the *S*-adenosylmethionine group who suffered from major depression with psychotic features (somatic/nihilistic delusions) were fully recovered by the end of the study; each had a Hamilton score of less than 10. Both of the imipramine patients with psychotic features failed to respond to imipramine only; one subsequently responded to the addition of a neuroleptic and the other to ECT. None of the patients became manic during the trial.

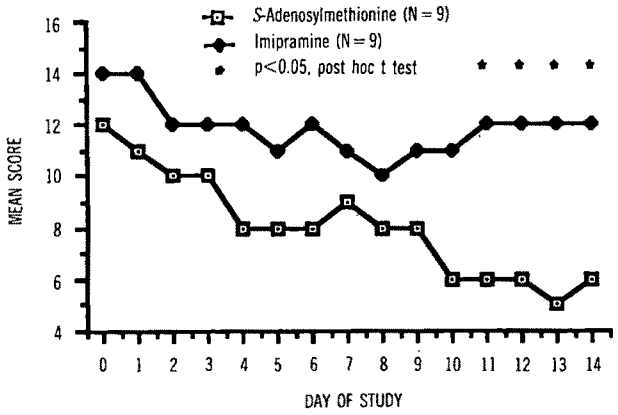
TABLE 1. Significant Differences Between End Point Depression Scores of Nine Patients Treated With *S*-Adenosylmethionine and Nine Patients Treated With Low Doses of Imipramine

Hamilton Depression Scale Item	Score at End of Treatment: *S*-Adenosylmethionine Mean	SD	Imipramine Mean	SD	t^a (df=16)	p
Suicide	0.1	0.3	1.0	1.1	2.3	<0.05
Initial insomnia	0.3	0.5	1.6	0.9	3.6	<0.01
Delayed insomnia	0.2	0.4	1.3	0.9	3.4	<0.01
Anhedonia	0.7	1.1	2.0	0.7	3.0	<0.01
Psychic anxiety	0.8	0.7	2.1	0.6	4.5	<0.001
Helplessness	0.4	0.7	1.9	1.3	3.0	<0.01
Worthlessness	0.4	0.7	2.0	1.4	2.9	<0.01
Hypersomnia	0.1	0.3	0.9	0.9	2.4	<0.05

[a]With Bonferroni correction.

A trend toward fewer side effects with *S*-adenosylmethionine treatment than with imipramine treatment was observed ($F=3.9$, $df=1, 16$, $p=0.06$); there was no significant Day by Treatment interaction. Trend analysis demonstrated that only the linear component was significant and a significant Day by Treatment interaction was present ($F=6.79$, $df=1, 16$, $p<0.02$). When we used the less conservative t test with Bonferroni adjustments, patients who received *S*-adenosylmethionine reported significantly fewer side effects on days 10 through 14 than patients who received imipramine ($t=2.3$ to 3.5, $df=16$, $p<0.04$) (see figure 2). The *S*-adenosylmethionine patients offered no spontaneous complaints of side effects. Three of these patients admitted to mild nausea only after direct questioning. The patients who received *S*-adenosylmethionine did not admit to any palpitations, restlessness, dizziness, or increased anxiety. There were no changes in any of the baseline laboratory values when laboratory tests were repeated at the end of the study. Measurements of vital signs were unchanged throughout the study, including those obtained during the infusions. There was no localized erythema at the site of the infusion.

FIGURE 2. Scores on the Somatic Symptom Checklist of Depressed Patients Receiving *S*-Adenosylmethionine or Imipramine[a]



[a]F=3.8, df=1, 16, p<0.06.

DISCUSSION

It appears that *S*-adenosylmethionine is a rapid and effective treatment for major depression and has few side effects. The procedure took 20 minutes to complete and was well tolerated by most patients. As far as we know, this is the first controlled, double-blind study to have been completed in the United States, and it confirms earlier reports from Europe regarding the efficacy and safety of *S*-adenosylmethionine.

It has been reported in a series of double-blind, controlled studies conducted in Europe (3–10) that *S*-adenosylmethionine produces rapid and marked clinical improvement in depressed patients when given parenterally. In addition, *S*-adenosylmethionine was reported by Lipinski et al. (11) to have been effective in seven of nine depressed patients treated in an open trial in the United States. Onset of drug action is said to be rapid: some patients experience complete remission of symptoms within a few days and most within 2 weeks (3–11). The drug is also reported to have no significant side effects except for the induction of mania in patients with bipolar illness (5, 8, 11). Mild nausea, restlessness, and moderate increases in anxiety have been reported in a small number of patients (3). Two-thirds of our patients treated with parenterally administered *S*-adenosylmethionine demonstrated a positive treatment response within 10 days. Scores on specific core depression items (depression, guilt, suicide, insomnia, anhedonia, psychic anxiety, and anergia) significantly improved, as was also reported in the European studies. The drug did not cause the worsening in psychic anxiety symptoms that has been previously reported (3); those symptoms actually improved in our patients.

Previous studies have shown that a few patients became manic or hypomanic when taking *S*-adenosylmethionine (8, 11). None of our patients became manic or hypomanic during the trial of *S*-adenosylmethionine, which is possibly a reflection of the paucity of bipolar depressed patients (only one patient with a history of mania was included in the study, and this patient received imipramine).

Since no placebo control group was included, the conclusions of this study are limited by our comparison group. The actual placebo response rate may be suggested by the results of a parallel study by Joseph Lipinski and John M. Davis. They observed that none of the five patients taking placebo but three of the six patients taking *S*-adenosylmethionine had a more than 50% improvement in scores on the Hamilton depression scale (reported at the First Italo/American Meeting on Alcoholism, Trieste, Italy, May 20, 1987). We gave the imipramine by slowly building up the dose over 7 days to 150 mg/day. Imipramine is frequently administered in doses up to 300 mg/day, and it can be argued that 2 weeks of imipramine at a relatively low dose is not sufficient to obtain an antidepressant response. Higher doses of imipramine for 4 weeks would be expected to produce a 70% improvement (12); however, this degree of improvement was seen by the 10th day of treatment with *S*-adenosylmethionine. Nevertheless, a study comparing the efficacy of intravenous *S*-adenosylmethionine and higher doses of imipramine seems indicated.

Another potential limitation of our study is that the efficacy of intravenous *S*-adenosylmethionine was compared to that of an orally rather than an intravenously administered antidepressant. However, in a recent World Health Organization study that compared intravenous and oral tricyclic antidepressants (13), no advantage of the intravenous method of administration was found.

The mechanism of action of *S*-adenosylmethionine in depression is unclear. However, recent pharmacological studies indicate that the drug has some similarities to standard antidepressants. It has been shown that *S*-adenosylmethionine crosses the blood-brain barrier after parenteral administration and causes a rise in its concentration in the CSF (14). In addition, it has been reported that this drug significantly increases CSF levels of homovanillic acid and 5-hydroxyindoleacetic acid, the metabolites of dopamine and serotonin, respectively, and lowers serum prolactin levels (14, 15). No changes in the concentrations of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol in plasma or CSF have been reported with *S*-adenosylmethionine. However, after chronic administration, *S*-adenosylmethionine appears to dampen the increase in plasma norepinephrine induced by orthostatic challenge in a manner similar to that seen with the monoamine oxidase inhibitor clorgyline (16). Thus, *S*-adenosylmethionine appears to blunt peripheral noradrenergic responsivity after chronic administration while increasing the central turnover of dopamine and serotonin.

We demonstrated that *S*-adenosylmethionine was superior to low-dose imipramine within the limits of this 14-day study, suggesting a more rapid onset of action of the drug. This characteristic of the drug may be a considerable advantage, considering the known

risk of suicide during the early phase of treatment with tricyclic antidepressants. Further, there is a trend in the United States for shorter inpatient hospital stays, which makes a rapidly acting antidepressant still more desirable. In such situations, intravenous *S*-adenosylmethionine may be an effective antidepressant, an alternative to ECT, and a useful drug for patients intolerant to the side effects of standard antidepressants. Further evaluation of this novel compound is certainly warranted.

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A Randomized Clinical Trial of Inpatient Family Intervention, III: Effects at 6-Month and 18-Month Follow-Ups

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This paper focuses on the follow-up results of a randomized clinical trial of inpatient family intervention (IFI) that emphasized psychoeducation. Results for the sample of 169 psychiatric patients suggested that adding family treatment to standard hospital treatment was effective; however, the statistical interactions indicated that this therapeutic effect was restricted to female patients with schizophrenia or major affective disorder. The effect of family treatment on male patients with these diagnoses was minimal or slightly negative. In a group of patients with other diagnoses, the Treatment by Sex effect was reversed: male patients did better with the family treatment.

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Inpatient family treatment is widely used on acute care psychiatric units (1–6), but to date there has been very limited evidence from controlled research that it is effective (7, 8) and no evidence that it affects one type of patient more than another. Our research aimed to fill this gap by studying one such treatment, broadly representative of the genre, which we called inpatient family intervention (IFI). The treatment was delivered in the way it is typically done on such a unit: for a wide range of patients, in combination with medication, and as part of an inpatient treatment program that does not necessarily extend to posthospital care. The results of this intervention at the time the subjects were discharged were presented in a previous report (9). There was a treatment effect favoring inpatient family intervention in the total sample, due primarily to better outcome in the female patients with major affective disorder who received family treatment. For male patients who received family treatment there was no effect or a relatively worse outcome at discharge. We present here the results for the whole sample at 6- and 18-month follow-ups. Subsequent reports will examine in detail the results for schizophrenic patients and patients with major affective disorder.

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METHOD

This research was done on an acute care unit of the Payne Whitney Clinic. Its methodology is described elsewhere in detail (9) and is summarized here. One hundred eighty-six subjects and their families met inclusion criteria (9) and signed informed consent forms. The patients were classified by *DSM-III* axis I criteria into four diagnostic groups: 1) schizophrenic/schizophreniform disorder with good prehospital functioning over the preceding 18 months, 2) schizophrenic/schizophreniform disorder with poor prehospital functioning over the preceding 18 months, 3) major affective disorder, and 4) other *DSM-III* axis I diagnoses. Within each of these groups, patients were randomly assigned to either standard hospital treatment with family intervention or standard hospital treatment without family intervention (comparison group). The two treatments were described in the report on discharge results (9); inpatient family intervention is a family treatment that emphasizes education about the nature of the illness and its treatment. The family treatment and comparison groups were compared on certain demographic variables and on pretreatment baseline measures (9). The two groups were equivalent, except that in the comparison group there were more people who were married or had been previously married. Medication was partially controlled to ensure that the patients in both groups received about equal amounts of the medications appropriate to their diag-

noses. Patients were assessed at admission, at discharge, after 6 months, and after 18 months, from the vantage points of the patient, a significant other, and an independent assessor, on global outcome, symptoms, and role functioning (work, family, social, and leisure time). Family attitudes toward treatment, social support, the patient, and family burden were also measured. We have previously described (9) several of the scales that were used and their functions: the Global Assessment Scale (GAS) (10), the Psychiatric Evaluation Form (11), the Family Attitude Inventory (9, 12), and the Goals of IFI Rating Scale (9).

The Role Performance Treatment Scale (13), which was not used at discharge and which we have not described before, was also used at the 6- and 18-month follow-ups. It assesses the patient's level of functioning over a variable length of time (up to 18 months) in each of the following role categories: primary/work (including school and home management), family, social, and leisure activities. Ratings are based on data gathered with a semistructured interview/rating guide; interrater reliability coefficients range from 0.82 to 0.99. A cutoff score on this scale was also used to categorize schizophrenic patients by preadmission functional level (unpublished manuscript by Spencer et al.).

At the end of the 18-month follow-up period, a research diagnosis was made in which we used all the information available at that point. The admission diagnosis was revised when necessary; 1) the diagnoses of 13 of 55 patients were changed from affective to schizophrenic disorder, 2) the diagnoses of seven of 78 patients were changed from schizophrenic to affective disorder, and 3) the diagnoses of six of 36 patients with other diagnoses were changed to affective disorder, and nine of 36 other diagnoses were changed to schizophrenic disorder. We used the research diagnoses in all data analyses because they were made on the basis of more complete information. An independent analysis in which the clinical admission diagnoses were used showed no substantive differences in the conclusions.

Seventeen of the original 186 patients (13 family treatment and four comparison) were dropped from the study during the course of hospitalization because their stays were too short for the requisite minimum amount of treatment to be delivered. At 6-month follow-up we obtained data on 168 of the 169 patients who completed treatment (79 family intervention patients and 89 comparison patients). At 18-month follow-up, we obtained data on 158 patients (77 family treatment and 81 comparison). In a few cases (five at 6 months and nine at 18 months) we were unsuccessful in obtaining a portion of the family data. The low attrition rate (6.5%; 11 of 169) and the characteristics of the family treatment and comparison group dropouts indicated that differential attrition did not reduce the comparability of the two groups.

The study design included several independent variables (treatment assignment, diagnosis, and sex) and several (dependent) outcome variables for both the patients and the families. We reduced the dependent variables to composite outcome measures by means of a principal-components analysis (14). This produced two patient outcome composite measures, one derived from the measures of global functioning and symptoms and the other derived from the measures of role functioning (which accounted for 44% and 11% of the variance in outcome, respectively, at 18 months). There were also two family outcome composite measures, one derived from the Family Attitude Inventory scales for attitude toward treatment and openness to social support and one derived from the patient rejection and family burden scales (which accounted for 26% and 43% of the variance in outcome, respectively, at 18 months). The multiple independent variables were then included in "higher order" (three-way) analyses of covariance (ANCOVA), which tested the main effect of treatment assignment on each composite at each follow-up point, along with the two- and three-way interaction effects with sex and diagnosis (see tables 1 and 3). These higher order analyses with composite outcome measures provided an experimentwise control of significance testing (15).

In addition to the higher order analyses on composites, we performed ANCOVAs on the individual outcome measures. Differences between the family intervention and comparison groups on these measures are presented in tables 2 and 4 as effect sizes, computed as correlation ratios (16, 17) that express the degree of relationship between treatment assignment and outcome; amount of outcome variance on a particular measure that is due to treatment group membership is equivalent to the value of r^2 (tables 2 and 4). The experimentwise higher order analyses on composite measures allowed us to test each of these many individual effect sizes for significance without the risk of type I error. Any significant treatment effect on an individual outcome measure that contributes to a significant effect in the higher order analyses of composites can be taken as valid; it contributes to a significant experimentwise result and is therefore "protected" against the charge that it is a chance finding in multiple significance tests (15, pp. 162–165). It is appropriate in an exploratory study to note any findings that may be relevant clinically and that suggest avenues for further research. We therefore summarize findings that attained statistical significance at the $p<0.10$ level (16, 18).

RESULTS

Outcome for Patients

The results of the three-way analyses for the patients' composite measures and the individual outcome measure effect sizes appear in tables 1 and 2. At 6 months there was a main effect of treatment on the

TABLE 1. Analyses of Outcome of Psychiatric Patients in a Study of Inpatient Family Treatment

Analysis of Covariance	6-Month Follow-Up						18-Month Follow-Up					
	Global Functioning/Symptoms			Role Functioning			Global Functioning/Symptoms			Role Functioning		
	F	df	p	F	df	p	F	df	p	F	df	p
Treatment	3.67	1	0.06	0.66	1	n.s.	0.91	1	n.s.	0.71	1	n.s.
Sex	3.99	1	0.05	1.30	1	n.s.	1.93	1	n.s.	2.11	1	n.s.
Diagnosis	6.86	3	0.0001	12.80	3	0.0001	9.84	3	0.0001	15.62	1	0.0001
Treatment by Sex	0.41	1	n.s.	0.02	1	n.s.	2.88	1	0.09	1.37	1	n.s.
Treatment by Diagnosis	0.05	3	n.s.	1.53	3	n.s.	1.15	3	n.s.	0.55	3	n.s.
Sex by Diagnosis	0.11	3	n.s.	0.22	3	n.s.	0.66	3	n.s.	0.41	3	n.s.
Treatment by Sex by Diagnosis	4.09	3	0.008	2.24	3	0.09	2.08	3	0.10	0.48	3	n.s.
Covariate				29.68	1	0.0001				22.36	1	0.0001

TABLE 2. Effect Sizes of Individual Measures of Outcome for Psychiatric Patients in a Study of Inpatient Family Treatment

Composite[b] and Individual Measures	Effect Size[a]					
	6-Month Follow-Up			18-Month Follow-Up		
	All Patients	Female Patients	Male Patients	All Patients	Female Patients	Male Patients
Global functioning/symptoms						
GAS score	0.16[c]	0.19[d]	0.10	0.12	0.20[d]	0.01
Patient Evaluation Form overall severity score	0.07	0.11	−0.01	0.05	0.13	−0.06
Grandiosity	−0.02	0.04	−0.09	−0.06	0.01	−0.17
Disorganization	0.11	0.14	0.07	0.01	0.09	−0.11
Withdrawal	0.16[c]	0.09	0.21[d]	0.09	0.11	0.05
Subjective distress	0.03	0.09	−0.06	0.00	0.06	−0.07
Role functioning (Role Performance Treatment Scale)						
Social	0.05	0.02	0.10	0.05	0.11	−0.01
Family	0.03	0.04	−0.01	0.09	0.10	0.07
Work	0.07	0.04	0.09	0.05	0.17	−0.13
Leisure	0.05	0.009	0.09	0.06	0.12	−0.01

[a]Positive values indicate better outcome with inpatient family intervention; values preceded by a minus sign indicate better outcome with comparison treatment. Values represent analysis of variance on residual change scores, computed as the deviation from the regression line describing scores at discharge as a function of scores at admission. Effect sizes are correlation ratios (r). $r=\sqrt{\frac{F(df \text{ for effect})}{F(df \text{ for effect})+df \text{ for error}}}$

[b]Results on each individual measure contributed to results on the associated composite measure.

[c]$p<0.05$.

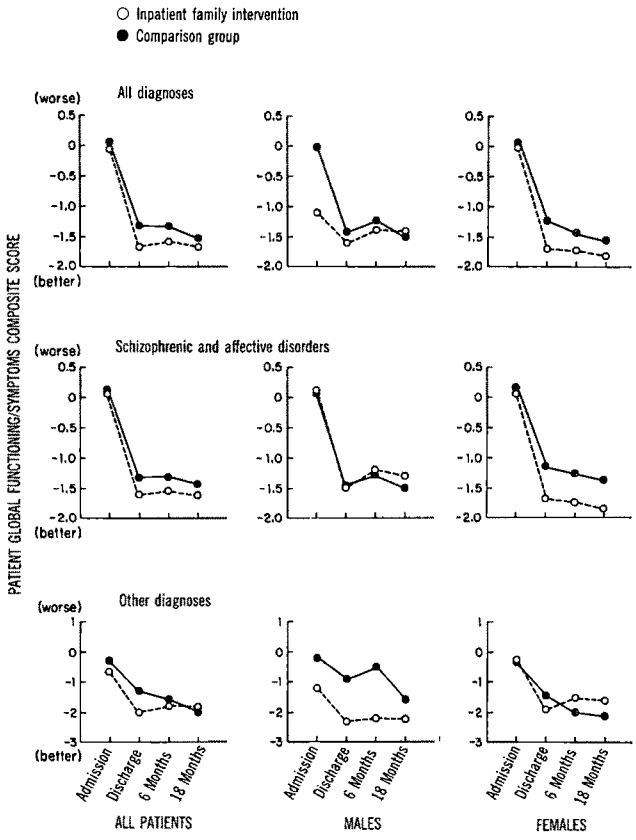
[d]$p<0.10$.

global functioning/symptoms composite measure. The effect sizes on individual measures (table 2) indicate that family treatment was favored, and the effect was greater and more consistent in female patients. There was also a Treatment by Sex by Diagnosis effect for this measure. Inspection of the composite means for Treatment by Sex by Diagnosis cells indicates that female patients in both the schizophrenic and affective disorder groups had a better outcome with family treatment, while male patients showed little effect. In the group with other diagnoses, the results were quite different: at 6 months the female patients given the comparison treatment had better outcomes, and the male patients did better with family treatment.

At 18 months there were no main effects of treatment, but there was a Treatment by Sex effect, and it was again the females in the family treatment group who showed a positive effect on all individual measures and on composite means. Again, there was a Treatment by Sex by Diagnosis effect on this composite; cell means indicate that female patients with schizophrenic or affective disorders did better with family treatment, while female patients with other diagnoses had a worse outcome with family treatment. Outcome on global functioning/symptoms is presented graphically in figure 1, where the differences at 6 and 18 months between the patients with major psychoses and those with other diagnoses are clearly seen.

At 6 months there was no main effect of treatment on the role functioning composite measure, but there was a Treatment by Sex by Diagnosis effect. The composite means show that female patients in the poorer functioning schizophrenic group did better with family treatment, while male patients showed little effect; among the better functioning schizophrenic patients, the comparison group male patients had a better out-

FIGURE 1. Outcome on Global Functioning/Symptoms of Psychiatric Patients in a Study of Inpatient Family Treatment



come, while the female patients showed little effect. Family intervention had no effect on either sex in the affective disorder group. The males who had other diagnoses did better with family treatment, while the females showed less effect.

At 18 months there was no significant treatment effect on role functioning.

In order to obtain a rough estimate of the *clinical* significance of the effect of family treatment, we used a cutoff score of 60 on the GAS to divide the entire sample into better and worse outcome groups at each follow-up point. A score of 61 on the GAS represents "moderate symptoms . . . or generally functioning with some difficulty," i.e., what clinicians might view as an average expectable state for patients who have been hospitalized for psychotic illnesses that are often chronic or recurrent. Comparison of the two treatment groups revealed a higher proportion of patients who had family treatment than of comparison patients in the better outcome group at 6 months ($\chi^2=5.29$, df=1, $p<0.02$) and at 18 months ($\chi^2=3.23$, df=1, $p<0.07$).

Outcome for Families

Family outcome is shown in tables 3 and 4. At 6 months there was a treatment main effect favoring family treatment on the composite measure of attitude toward treatment/openness to social support; it was similar for male and female patients. There were no treatment (main or interaction) effects on this measure at 18 months.

At 6 months there was a Treatment by Sex effect on the patient rejection/family burden composite measure, which favored families of females who received family treatment, and also a Treatment by Diagnosis effect. Composite means showed that family treatment was somewhat better for the families of patients (primarily females) with the major psychoses, while families of patients with other diagnoses did better without family treatment. At 18 months the only treatment effect on patient rejection/family burden was a Treatment by Diagnosis interaction similar to the interaction at 6 months.

At discharge the families of the family treatment patients were rated on achievement of their individualized goals for that treatment, which had been set at admission (9). Positive correlations were found between the family's overall achievement of goals and the patient's outcome on global functioning/symptoms at 6 months ($r=0.35$, df=64, $p<0.002$) and 18 months ($r=0.26$, df=64, $p<0.02$) and on role functioning at 6 months ($r=0.22$, df=64, $p<0.04$) and 18 months ($r=0.23$, df=64, $p<0.03$). Achievement of the goals of family intervention also correlated with outcome on the family attitude toward treatment/openness to social support composite at both 6 months ($r=0.21$, df=64, $p<0.05$) and 18 months ($r=0.35$, df=64, $p<0.002$).

Results for Diagnoses Other Than Schizophrenia and Affective Disorder

Patients with schizophrenia and major affective disorder were the study's primary clinical and research interest. The "other" diagnosis was a residual category that included all patients not diagnosed as having one of the major psychoses. Because this group was heterogeneous (including small numbers of patients with diagnoses such as substance abuse, dysthymic disorder, and organic mental disorder) and may not be exactly comparable to a particular population in other hospitals, the results for this group are harder to interpret and not easily generalized to other settings. However, we can say that our other diagnoses group made a significant contribution to a three-way interaction (Treatment by Sex by Diagnosis) on both of the composite measures for patients. There was a difference between male and female responses within this group (see figure 1) in that female family treatment patients had a worse outcome than their comparison group counterparts at both follow-up points and on both composite measures; this represents a striking reversal of the predominant finding in the groups with major psychoses, where the female patients did *better* with family treatment (figure 1). On family composite

TABLE 3. Analyses of Outcome for Families of Psychiatric Patients in a Study of Inpatient Family Treatment

Analysis of Covariance	6-Month Follow-Up						18-Month Follow-Up					
	Attitude Toward Treatment/Openness to Social Support			Patient Rejection/Family Burden			Attitude Toward Treatment/Openness to Social Support			Patient Rejection/Family Burden		
	F	df	p	F	df	p	F	df	p	F	df	p
Treatment	3.63	1	0.06	0.25	1	n.s.	2.03	1	n.s.	0.40	1	n.s.
Sex	0.49	1	n.s.	0.20	1	n.s.	0.11	1	n.s.	2.83	1	0.10
Diagnosis	10.19	3	0.0001	4.19	3	0.007	3.63	3	0.01	3.10	3	0.03
Treatment by Sex	0.12	1	n.s.	4.07	1	0.05	0.46	1	n.s.	1.50	1	n.s.
Treatment by Diagnosis	1.62	3	n.s.	2.59	3	0.06	0.98	3	n.s.	2.75	3	0.05
Sex by Diagnosis	0.50	3	n.s.	1.48	3	n.s.	0.75	3	n.s.	1.61	3	n.s.
Treatment by Sex by Diagnosis	0.98	3	n.s.	0.43	3	n.s	1.42	3	n.s.	1.33	3	n.s.
Covariate	59.77	1	0.0001	40.21	1	0.0001	48.79	1	0.0001	22.73	1	0.0001

TABLE 4. Effect Sizes of Individual Measures of Outcome for Families of Psychiatric Patients in a Study of Inpatient Family Treatment

Composite[b] and Individual Measures (Family Attitude Inventory)	Effect Size[a] for Families					
	6-Month Follow-Up			18-Month Follow-Up		
	All Patients	Female Patients	Male Patients	All Patients	Female Patients	Male Patients
Composite 1						
Attitude toward treatment	0.17[c]	0.14	0.20[d]	0.04	0.09	−0.01
Openness to social support	−0.15	−0.11	−0.20	0.06	−0.03	0.13
Composite 2						
Patient rejection	−0.03	0.04	−0.14	−0.02	0.07	−0.13
Family burden	−0.01	0.18	−0.04	0.11	0.24[d]	−0.05

[a]Positive values indicate better outcome with inpatient family intervention; values preceded by a minus sign indicate better outcome with comparison treatment. Values represent analysis of variance on residual change scores, computed as the deviation from the regression line describing scores at discharge as a function of scores at admission. Effect sizes are correlation ratios (r). $r=\sqrt{\frac{F(df \text{ for effect})}{F(df \text{ for effect})+df \text{ for error}}}$

[b]Results on each individual measure contributed to results on the associated composite measure.

[c]$p<0.05$.

[d]$p<0.10$.

measures, the group with other diagnoses showed no clear-cut sex effect nor any clear and consistent differences from the groups with schizophrenia and affective disorder.

Summary of Results

Results at discharge from the hospital (9) showed that inpatient family intervention's positive effect in the acute phase was primarily on female patients with affective disorder and on their families. At the later follow-up points presented here, the advantage for female patients persisted, but the positive effect was seen in schizophrenic patients as well as those with affective disorders. In contrast, in the heterogeneous residual group of patients with other diagnoses, the female patients in the comparison group did better than the females treated with inpatient family intervention at both 6 and 18 months.

At 6 months there was an effect favoring family treatment on attitude toward treatment and openness to social support for the families of patients with all diagnoses. At both 6 and 18 months there was an effect favoring family treatment on patient rejection and family burden for families of female patients with the major psychoses.

DISCUSSION

We chose a research design for this study that reproduced actual clinical conditions, although we recognized that this entailed problems. Several problems relating to the study of inpatient psychosocial treatments were identified in our previous paper on discharge results (9) and are not discussed here. We must be cautious in evaluating results from a large and complex study and ask whether there are alternative explanations for the treatment effects. When data are obtained on more than one diagnostic group and on a variety of outcome measures at more than one time point, there are attendant dangers in statistical analysis. Our method of data analysis was designed to protect against the possibility that the findings would be

statistical artifacts. Other sources of error in interpreting the apparent effects of inpatient family intervention might be confounding factors that could account for differences between the treatment groups. Baseline clinical differences were included as covariates in our analyses. Marital status was the one demographic variable not well-balanced in the randomization process (9); there were proportionately fewer married patients in the family treatment group than in the comparison group, but it seems unlikely that this was a positive prognostic factor which accounted for the better results in the family treatment group. We have previously explained (9) why we do not think there were confounding factors introduced during the treatment phase.

Posthospital treatment. In our research design, posthospital treatment was not controlled, since it is not usually provided and controlled by acute care inpatient units. Aftercare was allowed to vary as it would under normal clinical conditions. One of our hypotheses was that inpatient family intervention would affect patient/family participation in aftercare. This design was chosen for practical reasons (it is hard to provide and control posthospital treatment for 18 months in a study with a large number of subjects) and because it was clinically realistic; but the design presents scientific problems. The quantity and type of aftercare over a period of 6 or 18 months, even if affected by the inpatient treatment, will also vary among patients because of uncontrolled factors. This makes it harder to demonstrate statistically the longer-run effects of an *inpatient* intervention. There is also a commonly held belief that hospital treatment results begin to "wash out" during the months after discharge. Under these scientific and clinical constraints, the positive results that we found for inpatient family intervention are particularly noteworthy.

As would normally be done, outpatient follow-up treatment was recommended at the time of discharge to patients and their families in both the family treatment and comparison groups. Recommendations were made to families of the comparison group patients by the primary therapist, and these included recommendations for family treatment if this appeared to be indicated. At 6 and 18 months we gathered information on the posthospital treatment experience of the entire sample. Most of the schizophrenic and affective disorder patients took medication during the postdischarge period, and many patients participated in one or more of the following types of treatment: individual psychotherapy, group therapy, vocational rehabilitation, self-help support groups, and family therapy. When the inpatient family intervention and comparison groups were compared with regard to their participation in each of these different types of treatment, the number of statistically significant differences was not much greater than would be expected by chance. In addition, with the one important exception of outpatient family treatment, these differences were not such as to have contributed to the outcome differences found at 6 and 18 months. The proportion of patients involved in posthospital family treatment at 6 months and the mean amount of time spent by those in family treatment at 18 months were higher for the inpatient family intervention group. This aftercare difference is not an alternative explanation for our findings unless it occurred by chance. It is more likely a result of the inpatient family therapy—an intervening variable rather than a confounding variable.

Time of effect. Most hospital psychiatrists probably view family treatment as an inpatient modality that will influence the posthospital course; change in family attitudes or behavior is more likely to affect the patient after his or her return to family and community. The wider range of inpatient family treatment effects at follow-up than at the time of discharge confirmed this expectation. It also suggests that studies of the impact of inpatient treatment should evaluate outcome at different, later time points, not just at the time of discharge from the hospital; effects do not "wash out" in any simple way during postdischarge months.

Mechanism of effect. It seems likely that inpatient family treatment changes family attitudes and that this in turn affects the patient's outcome. This explanation of the treatment effects is compatible with our data, but it is not proven by the design of this study. The family treatment (which includes the patient in the sessions) may have a positive effect on the *patient*, which in turn has a positive effect on family attitudes toward the patient and/or the treatment. The evidence (from correlations) that patients whose families achieve individual family goals while the patient is in the hospital do better at follow-up is not definitive; it may be that there is a common family/patient factor which accounts for both patient and family response to inpatient family treatment. We can only conclude here that the effects of inpatient family intervention in general are positive for female patients with the major psychoses and for their families. Likewise, our analyses afford no explanation of the sex difference in response to family treatment; we speculated earlier (9) on some possible explanations.

CONCLUSIONS

Schizophrenia and major affective disorder account for a large proportion of the disorders of patients on acute care psychiatric units. In acute psychotic episodes it is not always possible to distinguish at admission between the two. The general conclusion that inpatient family intervention is likely to be helpful for a female patient with either of these major psychoses should probably be an initial guiding principle in planning treatment. This may not be the case for male patients. There is evidence that female patients with other diagnoses may do better without the treatment.

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Four-Year Evaluation of a Psychiatric Clerkship: 1982–1986

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The authors describe a psychiatric clerkship organized to achieve goals relevant to all medical students, regardless of their future specialty choice. The clerkship had been in place for 8 years in 1986, and standardized program evaluations were available for 4 years. A survey of the diverse clinical settings used for the clerkship showed that each had unique strengths and weaknesses but that each could meet the core goals of the clerkship, indicating that this clerkship design would also be feasible in a smaller department with any one or two of the settings available.

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Development of psychiatric services in general hospital and community-based programs has moved the psychiatric patient increasingly into the care of the nonpsychiatric physician. Changes in health care delivery have important consequences for planning medical student education in psychiatry, particularly for the future physician who will be called on frequently by nonphysician mental health care providers to supervise clinical evaluation and psychotropic medication in managed health care facilities. A large proportion of medical patients have serious emotional problems (1); therefore, adequate preparation in psychiatry must be provided to all future physicians. Hull (2) noted that many nonpsychiatric physicians already regard their preparation in psychiatry as inadequate. Medical students must be taught to focus on the patient as a person rather than to place exclusive emphasis on diagnosis of disease through an inventory of physical signs, symptoms, and laboratory findings (3).

In this paper we will describe a basic psychiatric clerkship model designed to emphasize the needs of the nonpsychiatric physician for psychiatric knowledge and skills. This model closely approximates the 1982 recommendations of the Committee on Medical Student Education of APA (4) and provides a practical trial of a clerkship similar to the one envisioned by that committee. In 1986, this clerkship had been in place for 8 years (1978–1986) at Yale University School of Medicine, where a large, diverse psychiatry department has provided a "laboratory" in which the clerkship model has been tested in a variety of clinical settings. This experience has demonstrated that the clerkship adapts to several types of clinical settings; therefore, it would also be suitable for departments having a limited number of settings.

Before 1978 different models of clerkship teaching had evolved in Yale's psychiatry department reflecting the diversity in services and faculty. The 11 clinical settings used for medical student clerkships differed in respect to institution (a general hospital, a Veterans Administration [VA] hospital, and a mental health center), length of patient stay, patients' socioeconomic and psychopathological characteristics, and institutionally preferred modes of treatment. Students learned different subspecialty realms of psychiatry that had evolved from specialized practice paradigms. No stated goals or objectives unified the clerkship teaching. The only central activity common to all was a once-a-week didactic seminar led by the clerkship director.

In 1978 an evaluation of the clerkship led to the conclusion that students were not acquiring core skills and knowledge. A survey of students' narrative evaluations of the experience, a review of the students' written work, and interviews with service chiefs and with other faculty suggested that the special nature of each of the settings greatly influenced the skills and knowledge acquired by the students, that each assignment had strengths and weaknesses, and that the clerkships varied greatly along the dimension of student satisfaction. The teaching models could be grouped into four types: milieu, junior-resident, didactic, and consultation.

In a ward using a milieu approach, students reported feeling left out if asked only to observe but bewildered if expected to participate. Without an explicitly defined role or task, students experienced the clerkship as fascinating, anxiety provoking, or boring. Students questioned the sharing of responsibility among staff and the encouraging of patient input into decision making. Importantly, most viewed their experience in wards using a milieu approach as irrelevant to the rest of their medical careers.

The junior-resident model operated in evaluation/crisis units, where treatment was based on a team approach similar to clinical rotations in other medical specialties. Here students were asked to function as

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primary clinicians. Optimally, students could rapidly acquire knowledge and skills related to psychiatric treatment of the mentally ill patient. However, students reported often feeling overwhelmed and fearfully trying not to harm the patient. Students were especially apt to resort to use of rote learning or nonpsychiatric coping devices (i.e., sympathy or an attempt to assume a patient's problems). They frequently asked permission to curtail other educational activities to pursue patient care. Meeting the treatment needs of their patients left them little time to investigate the broad range of psychiatric problems. Although some students emerged from evaluation/crisis units feeling that "there's not much to being a psychiatrist," others left with the uneasy sense that psychiatry was too complex and mysterious for them. Unusually mature or knowledgeable students, especially those with previous psychiatric experience, performed with reasonable competence and were enthusiastic about their clerkship.

A didactic model of education developed when students were not assigned clinical responsibility. In settings where research was a prominent activity, education was emphasized to the exclusion of training, and students were either expected or encouraged to become involved in research tasks. Requirement of a research or clinical paper often separated students even farther from the patients. The strength of the didactic model was that it avoided exploiting students and offered them time to develop skills and interest in research and to present their ideas in a disciplined and scholarly way. However, the potential weakness was that students failed to acquire clinical skills and concrete knowledge; they lacked confidence in their ability to care for psychiatric patients.

In the consultation model students were assigned as full-time members of the psychiatric consultation-liaison team. This experience directly addressed the contribution of the psychiatrist to the care of the medically ill patient and illustrated how the psychiatrist could work closely with physicians from other specialties. Many authors, including Weddington et al. (5) and Griffin et al. (6), have suggested this as a useful model. Some problems were noted with this model, however. Although more involved with organic mental problems, students were less likely to perform a complete medical and psychiatric examination of the patient. Instead, students relied on other specialists. Patient contact was limited because the psychiatrist functioned as a consultant to specific patients. Often students adhered to the biomedical model, concerned with problems of diagnosis of organicity and drug effect, which are frequent in consultation practice. Because of practical inexperience, students were unlikely to be alert to or to benefit from the complexities of the consultant role. Additionally and perhaps most importantly, students missed the experience available on inpatient services of becoming comfortable working with more severely disturbed psychiatric patients.

THE MODEL

The challenge was to devise a basic clerkship to provide an opportunity to acquire a core set of skills and knowledge essential for the future physician that could be implemented in the wide variety of settings available. Examination of the 8 years of experience with the resultant model and the standardized evaluations in the last 4 years illustrates the advantages and drawbacks of each type of setting for this uniform clerkship design.

The basic 6-week clerkship is designed to supply 1) a specified and attainable body of skills and knowledge, 2) opportunities for direct patient contact (7), 3) experience in a role that relates clearly to the needs of future physicians, 4) exposure to clinical activities that are helpful to specific patients, 5) didactic exercises directed to the special and specific needs of the medical student, and 6) contact with teachers—residents, ward attending physicians, and senior clinicians—who have special interests in medical student education (8–11).

Psychiatrists are uniquely suited to teach certain skills and knowledge needed by every physician and attainable in the brief clerkship period: examining and assessing patients with emotional problems or mental illness, making a psychiatric diagnosis, handling psychiatric emergencies, using psychotropic drugs, recognizing indications for making referrals, and appreciating the interplay between psychosomatic and somatopsychic factors. The explicit requirements of this model are for each student to be able to 1) conduct a screening interview and record the chief complaint, psychiatric history, social history, developmental history, and medical history, 2) perform and write up the results of a physical examination, including a complete neurological and mental status examination, of an emotionally disturbed or mentally ill patient, 3) prepare a written discussion of a differential diagnosis based on information from the interview and the signs and symptoms observed during the physical and mental status examinations, 4) plan further evaluation to aid in choosing among diagnostic possibilities, 5) recommend initial treatment or referral, 6) assess whether dangers to or from a patient exist, and 7) discuss indications and procedures for lawful involuntary commitment of a patient to a mental hospital for treatment.

Design of the Clerkship

To achieve these goals in the 6 weeks available, students assess and plan treatment rather than carry out treatment. The center of the clerkship is the patient workup. Each student evaluates one patient each week, writes up that patient's case, and follows his or her course. The assessment consists of taking a psychiatric and medical history (including a review of systems) as well as conducting a physical examination (including a neurological examination).

Teaching is individualized for each student. The stu-

dent is supervised in the assessment of the patient by a resident on the service. The student spends at least 1 hour each week with a faculty tutor in a one-to-one review of the written workup. All aspects of that patient as a person are addressed, including social and psychodynamic issues. These case write-ups are used both for teaching and for evaluation of the student's work. A second weekly tutorial is held with a different faculty tutor who observes the student interviewing patients and addresses interviewing skills and medical aspects of history taking, especially the mental status examination.

Other educational activities include a weekly rotation through the psychiatric service of the emergency room to examine ambulatory patients in crisis (this rotation is supervised by residents and faculty, and the focus is on evaluating suicidal or homicidal patients), a half-day at a state hospital, a half-day at a geriatric facility, and a half-day at a forensic facility. Problems of patients who are sent out into the community to live are presented, since these patients will require medical as well as psychiatric care.

Formal didactic time is provided in weekly conferences addressing behavioral neurology, psychopathology and treatment modalities, and a survey of special topics such as alcoholism (12), drug dependence, geriatric psychiatry, and forensic psychiatry. The students attend case conferences on each service and are encouraged to present their patients.

Faculty Involvement

Faculty members are assigned to the basic clerkship from three groups, each with particular expertise. First, residents supervise student interviews and physical examinations and provide training in specific clinical skills. Second, full-time faculty of the inpatient service—psychiatrists, psychologists, psychiatric nurses, and psychiatric social workers—demonstrate the skills that they use in day-to-day treatment of patients as well as assist in teaching the formal didactic conferences. Third, both full-time and clinical faculty act as tutors for the weekly patient evaluation and write-up.

Senior faculty members give close individual supervision and offer students the security of being taught by experienced clinicians who are not burdened by their own need to learn. The need for a preceptorial relationship (11–13) and the importance of faculty as role models (2, 13) have been emphasized in the literature. Faculty who work most closely with the students on the core exercises—the case write-up tutor and the tutor for the interviewing sessions—are chosen from outside the service. Because the responsibility for teaching is shared among a large group of individuals, faculty who have commitments to research and practice can still participate meaningfully. The experience of working with a variety of teachers who are at different career levels aids students in evaluating psychiatry and psychiatrists and may correct previously held stereotypes.

One or two students are assigned to each setting for the entire 6-week clerkship on the basis of their preferences. Papernick et al. (10) argued for this choice as a positive experience of the clerkship. Of the 513 medical students who took the clerkship between 1981 and 1986, 405 (79%) received their first or second choice.

The core structure of the clerkship for students is the same regardless of the clinical setting, even though each setting contributes unique aspects to the rotation. On either the acute or longer-term inpatient unit, students function as data gatherers and observers rather than as junior resident psychiatrists. This provides students with a useful and necessary task directly related to patient care and also to their future roles. Although this offers patient contact, it does not impose responsibility for patient care that goes beyond the ability of the beginning clinician. The need for adequate supervision in clinical experience has been addressed by Bleier et al. (9) and Fox and Rosen (11).

The specialized clerkship models that were in place before 1978 were transformed into advanced elective clerkships available for students who were interested in psychiatry as a possible career and who wanted to learn about specific psychiatric treatment skills.

CLERKSHIP EVALUATION

The model psychiatric clerkship has been successful as reflected in ratings by students and the number of students who chose psychiatry as a future specialty.

Evaluation of the Students

At this medical school there are no required written examinations. Thus, there is no opportunity to compare scores before and after the clerkship or before and after the change in the teaching model. On all clinical services, evaluation of the student's problem-solving ability and fund of knowledge is accomplished by close work with faculty—tutors, residents, and chiefs of services. Each student's performance is described in a narrative and rated numerically on several items as well as given an overall rating. The case write-ups provide one sample of the student's work. Copies of the work-ups with the tutors' comments are returned to the clerkship director (L.W.R), who reviews the students' and tutors' work and thus monitors their quality. A survey of the settings indicated that honors ratings were distributed evenly across the department.

Overall Ratings by Students

Since 1982, comprehensive evaluations of all medical school clerkships have been distributed by the Office of Student Affairs: 365 (71%) of the 513 students who took the clerkship during 1982–1986 returned their evaluations. Seventy percent of these students rated the clerkship excellent or outstanding. Table 1 presents the ratings by year and clinical setting.

TABLE 1. Four-Year Ratings of Clerkship Settings by Medical Students at Yale University School of Medicine

Setting and Year	Rank[a]	Number of Students Rating Setting	Students Who Rated Setting Excellent or Outstanding	
			N	%
VA evaluation/crisis unit	1	51	46	91
1982–1983		14	14	100
1983–1984		14	12	86
1984–1985		13	11	85
1985–1986		10	9	90
Mental health center evaluation/crisis unit	2	48	43	90
1982–1983		8	6	75
1983–1984		14	13	93
1984–1985		12	10	83
1985–1986		14	14	100
General hospital milieu program 1	3	37	31	84
1982–1983		5	2	40
1983–1984		8	6	75
1984–1985		11	11	100
1985–1986		13	12	92
Mental health center research program	4	19	15	79
1982–1983		5	4	80
1983–1984		5	2	40
1984–1985		4	4	100
1985–1986		5	5	100
General hospital evaluation/crisis unit	5.5	40	28	70
1982–1983		11	9	82
1983–1984		11	4	36
1984–1985		9	7	78
1985–1986		9	8	89
Mental health center milieu program	5.5	47	33	70
1982–1983		11	11	100
1983–1984		17	11	65
1984–1985		10	6	60
1985–1986		9	5	56
VA milieu program 1	7	20	13	65
1982–1983		7	4	57
1983–1984		5	4	80
1984–1985		3	0	0
1985–1986		5	5	100
General hospital milieu program 2	8	23	12	52
1982–1983		10	6	60
1983–1984		6	3	50
1984–1985		3	1	33
1985–1986		4	2	50
VA consultation-liaison team	9	12	6	50
1982–1983		5	2	40
1983–1984		1	1	100
1984–1985		5	2	40
1985–1986		1	1	100
General hospital consultation-liaison team	10	50	22	44
1982–1983		13	5	38
1983–1984		11	5	45
1984–1985		16	7	44
1985–1986		10	5	50
VA milieu program 2	11	18	5	28
1982–1983		4	3	75
1983–1984		4	1	25
1984–1985		7	0	0
1985–1986		3	1	33
Total		365	254	70
1982–1983		93	66	71
1983–1984		96	62	65
1984–1985		93	59	63
1985–1986		83	67	81

[a]Based on percentage of students rating setting excellent or outstanding.

There were 44 median ratings (11 settings for 4 years) ranging from unacceptable to acceptable to good to excellent to outstanding. There were no ratings of unacceptable, one of acceptable, 14 of good, 25 of excellent, and four of outstanding. Over the 4 years only one setting received an overall median rating of less than good.

Although the model has been successful in a variety of settings, it may be best suited to evaluation/crisis units. These consistently were given high ratings. The primary didactic task of students—evaluating patients—is most congruent with the clinical goal of such units. In keeping with this, the consultation services ranked lowest overall. In intermediate ranks, other factors apply to particular students, such as the patient population or research orientation.

Student Evaluation of Clerkship

Students on all settings consistently gave high ratings to the individual tutorials, the emergency room experience, and the field trips. These didactic experiences are not dependent on a particular clinical setting. Narrative comments stressed the value of the field trips and of individual instruction by a number of faculty and resident teachers who had diverse expertise, philosophies, and approaches to patients. For every year rated, both the field trips and the individual instruction received median ratings of greater than 4 on a scale of 1 (worst) to 5 (best).

MEDICAL STUDENTS CHOOSING PSYCHIATRY AS A CAREER

Several (8, 13) authors have suggested that the clerkship strengthens preexisting positive attitudes and makes no change in negative attitudes toward choice of psychiatry as a career and that a positive clerkship experience clearly increases the number of students choosing this specialty.

One indicator for changes in attitude toward psychiatry in medical students during a clerkship is the difference between pre- and postclerkship ratings of psychiatry as a possible career. For 3 years, 1983–1986, 187 (62%) of 304 students ranked their future specialty choices (1=most likely to 10=least likely) before and at the end of the clerkship. Fifty-eight (31%) of these students ranked psychiatry first before the clerkship and 75 (40%) rated psychiatry first after the clerkship, 19 (10%) rated psychiatry as their first choice both before and after, and 14 (7%) applied for residencies in psychiatry when they were senior medical students. Eighteen (14%) of the 129 students who had not rated psychiatry as their first choice before the clerkship did so after; eight of these students applied for a psychiatric residency.

The experience of the 10 students who had ranked psychiatry first before the clerkship and ranked it lower after is also relevant; two of these students later

applied for a residency in psychiatry. Three students who received evaluations of honors or just short of honors rated it lower afterwards. Faculty comments on these students questioned their ability to work with psychiatric patients or staff. These three students did not choose psychiatry—apparently the clerkship had helped them decide that psychiatry was not a good specialty for them. The literature often emphasizes the influence of the clerkship for recruiting students to a particular specialty. The effect of helping students to match their interests and abilities to a specialty is equally important.

A consistently high number of Yale medical students have applied to the Yale residency program: 41 (10%) of the 413 graduates in 1984–1986. Thus, this clerkship design has not discouraged this specialty choice.

CONCLUSIONS

Our survey of the clinical settings available for medical students indicates that although each type of setting has unique strengths and weaknesses for teaching medical students, the core goals of a clearly defined clerkship emphasizing the psychiatric skills and knowledge that all physicians should acquire can be met in each of them. Although evaluation/crisis units seem best suited to implementation of this design, the general applicability and adaptability of this model is evident, indicating that it would be feasible for smaller departments.

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Personality Features of Obsessive-Compulsive Disorder

Russell T. Joffe, M.D., Richard P. Swinson, M.D., and Joseph J. Regan, Ph.D.

The authors evaluated personality dysfunction in 23 patients with primary obsessive-compulsive disorder and an age- and sex-matched group of patients with major depressive disorder. There were no significant differences between the two patient groups with respect to mean personality trait scores or the frequency or type of personality disorder diagnosis. A mixed personality disorder with avoidant, dependent, and passive-aggressive features was most commonly observed in the obsessive-compulsive group. There was a very low frequency of schizoid or compulsive personality disorder.

(Am J Psychiatry 1988; 145:1127–1129)

Obsessive-compulsive disorder is a chronic, recurrent illness that has an extremely poor prognosis. Although it had been assumed that individuals with compulsive personality disorder are predisposed to develop obsessive-compulsive disorder (1, 2), there are actually very limited data to support such a hypothesis (1–3). In fact, little attention has been paid in the literature to the systematic evaluation of the personality characteristics of patients with primary obsessive-compulsive disorder. Rasmussen and Tsuang (3) reported that patients with primary obsessive-compulsive disorder had a wide range of personality disorder diagnoses and that fewer than half satisfied criteria for compulsive personality disorder; however, they failed to use standardized assessments for diagnosing personality disorder and did not describe personality characteristics in addition to personality disorder diagnoses in their group of patients. Jenike et al. (4) described a subgroup of patients with primary obsessive-compulsive disorder who had features of schizotypal personality disorder and who were particularly refractory to standard treatment. They, however, failed to describe the personality characteristics of the remainder of their cohort of patients. We, therefore, carried out a systematic evaluation of the personality characteristics and the frequency of personality disorder diagnoses in a group of patients with primary obsessive-compulsive disorder. Furthermore, we studied a psychiatric control group of patients with primary major depressive disorder to evaluate the specificity of personality traits and disorder to primary obsessive-compulsive disorder.

METHOD

Patients (N=23) who fulfilled Research Diagnostic Criteria (RDC) (5) for primary obsessive-compulsive disorder on the basis of a structured interview during which the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (6) was completed consented to participate in this study. The evaluation of personality characteristics was one aspect of a larger assessment of the clinical and biological aspects of primary obsessive-compulsive disorder. Nine of the patients had a history of secondary major depressive disorder, but only four of the nine fulfilled RDC for current secondary major depressive disorder. All subjects were screened by routine laboratory and clinical examination for the absence of medical illness.

The comparison group comprised 23 patients with the lifetime diagnosis of primary major depressive disorder, unipolar subtype, according to the SADS-L. Each patient with primary obsessive-compulsive disorder was matched for age (within 2 years), sex, and presence of depression as determined by the SADS-L and the score, within 3 points, on the Beck Depression Inventory (7) with the next consecutive outpatient referred for affective illness to the Mood Disorders Clinic at St. Michael's Hospital.

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TABLE 1. Scores on the Millon Clinical Multiaxial Inventory Personality Scales of Patients With RDC Obsessive-Compulsive Disorder (N=23) or Major Depressive Disorder (N=23)

	Millon Inventory Score			
	Obsessive-Compulsive Patients		Depressive Patients	
Personality Scale	Mean	SD	Mean	SD
Schizoid	60.6	22.2	61.0	23.1
Avoidant	70.9	30.8	58.4	29.7
Dependent	68.0	33.9	57.9	30.7
Histrionic	45.8	25.6	49.2	24.5
Narcissistic	45.8	22.9	53.6	25.6
Antisocial	52.4	19.5	59.2	17.8
Compulsive	56.3	20.0	58.3	21.9
Passive-aggressive	65.8	36.4	60.1	33.9
Schizotypal	59.3	15.9	55.3	17.9
Borderline	67.5	23.2	60.1	19.6
Paranoid	53.2	17.6	54.4	18.2

There were 13 men and 10 women in each group. All patients were medication free for a minimum of 2 weeks before completion of the evaluation. In addition to the SADS-L and the Beck inventory, each patient completed the Millon Clinical Multiaxial Inventory (8), a 175-item self-report inventory that allows one to obtain personality trait scores and personality disorder diagnoses similar to those in *DSM-III* (9). The Millon inventory was constructed with normative data based on psychiatric rather than general populations to improve discrimination efficiency of scales and diagnostic accuracy. We used base rate rather than normalized standard score transformations to allow for the frequency of diagnoses to be roughly equivalent to representative clinical rates (8). One of the investigators (R.J.), blind to the scores on the Millon inventory, completed the Diagnostic Interview for Borderlines (10) for each patient within 1 week of the initial diagnostic assessment.

Personality trait scores on each of the 11 scales on the Millon inventory were obtained for individual patients. A score higher than 75 on any scale qualified that patient for the diagnosis of a particular personality disorder. Statistical analysis involved two-tailed t tests for continuous data and chi-square tests for categorical data when patients with major depressive disorder were compared with those with obsessive-compulsive disorder.

RESULTS

There was no significant difference in mean±SD age between the patients with obsessive-compulsive disorder (36.0±10.1 years) and those with major depressive disorder (36.5±10.4 years). There was also no significant difference between the two patient groups in the mean±SD scores on any of the 11 personality scales (table 1).

As most patients had scores of 75 or higher on more than one personality scale, they also had several personality disorder diagnoses (table 2). In the primary obsessive-compulsive disorder group, avoidant, dependent, and passive-aggressive personality disorder were the most common diagnoses. In fact, a mixed personality disorder with avoidant, dependent, and passive-aggressive features was the most common diagnosis (N=12). We found that only one of the 23 patients had a score that qualified for the diagnosis of compulsive personality disorder. Moreover, only four patients had evidence of a schizotypal personality disorder. There was no significant difference by chi-square test in the frequency of personality disorder diagnoses in the two patient groups.

TABLE 2. Frequency of Millon Clinical Multiaxial Inventory Personality Disorder Diagnoses in Patients With RDC Obsessive-Compulsive Disorder or Major Depressive Disorder[a]

	Obsessive-Compulsive Patients (N=23)		Depressive Patients (N=23)	
Personality Disorder Diagnosis	N	%	N	%
Schizoid	6	26.1	7	30.4
Avoidant	13	56.5	10	43.5
Dependent	13	56.5	8	34.8
Histrionic	4	17.4	2	8.7
Narcissistic	2	8.7	7	30.4
Antisocial	3	13.0	2	8.7
Compulsive	1	4.4	3	13.0
Passive-aggressive	14	60.9	10	43.5
Schizotypal	4	17.4	3	13.0
Borderline	9	39.1	6	26.1
Paranoid	4	17.4	2	8.7

[a]Patients had, in most cases, more than one diagnosis of personality disorder.

Four of the 23 patients with primary obsessive-compulsive disorder and three of the 23 patients with major depressive disorder had no personality disorder diagnosis. The mean number of personality disorder diagnoses was not significantly different between patients with primary obsessive-compulsive disorder (3.2±2.2) and those with primary major depressive disorder (3.1±3.3).

Six of the 23 patients with primary obsessive-compulsive disorder and five of the 23 patients with primary major depressive disorder qualified for the diagnosis of borderline personality disorder on the Diagnostic Interview for Borderlines. All patients with borderline personality disorder on the Diagnostic interview also were classified as having that diagnosis on the Millon inventory. The mean±SD Diagnostic interview scores were not significantly different between the primary obsessive-compulsive disorder group (4.9±2.1) and the primary major depressive disorder group (4.7±2.4).

DISCUSSION

Our data suggest that personality disorders are frequent in patients with primary obsessive-compulsive disorder and that the frequency of personality disorder

diagnoses is no different between patients with primary obsessive-compulsive disorder and other psychiatric patients, particularly those with primary major depressive disorder. Our patients with primary obsessive-compulsive disorder had a wide range of personality disorder diagnoses; in fact, a mixed personality disorder diagnosis was most frequently observed in these patients. We did not find a high prevalence of compulsive personality disorder in our obsessive-compulsive disorder group; rather, such a diagnosis was underrepresented, possibly because of underreporting of compulsive features on a self-report inventory like the Millon inventory.

Our findings differ somewhat from two recent studies (3, 4). Although Rasmussen and Tsuang (3) observed a range of personality disorder diagnoses in their cohort of patients with primary obsessive-compulsive disorder, they found that approximately half of their patients had compulsive personality disorder. The difference between our findings and theirs may be due to the fact that their method of ascertaining personality disorder diagnoses is not clearly specified. Our sample and that of Rasmussen and Tsuang (3) were clinical samples of patients most of whom had not been previously hospitalized. Jenike et al. (4) reported that almost one-third of their patients with primary obsessive-compulsive disorder also had a schizotypal personality disorder that made them refractory to treatment. Only 17.4% of our study sample had a diagnosis of schizotypal personality disorder. Although the difference between our finding and that of Jenike et al. (4) is not apparent, it may be related to the source of referral and the method of evaluation of personality disorder in these patients.

Our initial clinical impression that borderline personality disorder was overrepresented in patients with primary obsessive-compulsive disorder was not confirmed by the data. There was no significant difference in the frequency of borderline personality disorder between the patients with primary obsessive-compulsive disorder and patients with primary major depressive disorder as defined either by the Millon inventory or the Diagnostic Interview for Borderlines.

Our conclusions are limited by several methodological issues. First, our relatively small sample size precludes definitive conclusions about the range and distribution of personality disorders in patients with primary obsessive-compulsive disorder; moreover, the lack of difference in personality measures between the two groups may have resulted from a type II error due to our small sample size. Second, we have shown that the Millon inventory diagnoses of personality disorder are state dependent (R.T. Joffe and J.J. Regan, unpublished paper), but only four of our patients had a current major depression; therefore, the effects of depressed state on the diagnosis of personality disorder in our cohort appear to be limited. Furthermore, our finding that patients with primary obsessive-compulsive disorder did not differ from patients with primary major depressive disorder with respect to mean personality trait scores and frequency or distribution of personality disorder diagnoses is unlikely to be contaminated by the effects of depressed state because these patients were carefully matched for the presence of a current depressive episode and for severity of depression as measured by the Beck Depression Inventory.

Most of our patients had mixed personality disorder diagnoses, which accounts for the relatively high number of personality disorder diagnoses in both patient groups. The high number of diagnoses per patient on the Millon inventory may be seen as a weakness of the diagnostic utility of this instrument, but Millon has countered that the inventory reflects clinical reality because mixed personality disorder diagnoses are more common than single or pure personality disorders.

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A New and Timely Delusion: The Complaint of Having AIDS

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Delusions presented by patients with psychiatric disorders are often a combination of psychopathology and current events. The authors present three cases that document the delusion of having acquired immune deficiency syndrome (AIDS) in patients who were not members of high-risk groups but had psychiatric disorders. This clinical phenomenon raises psychodynamic issues as well as adds a new dimension to the controversy over AIDS testing.

(Am J Psychiatry 1988; 145:1130–1132)

Clinicians are aware of those delusions which are commonly seen. Nihilistic delusions, delusions of poverty, and somatic delusions are frequently mentioned in psychiatric texts as being characteristic symptoms of severe depressive disorders. Delusions of grandiosity, persecution, jealousy, and of being controlled, as well as hypochondriacal delusions, may be seen in patients with schizophrenic, manic, or paranoid disorders (1). The content of delusions varies tremendously and often represents an external focus for the patients' internal wishes and fears. It is common clinical experience that delusions tend to incorporate material which is of popular interest at the moment.

Acquired immune deficiency syndrome (AIDS) has become a topic of increasing public concern. There have been many media reports of the current human impact of, as well as the future prospects for, the syndrome. Some reports have been capable of eliciting fear if not outright panic.

While there have been reports (2, 3) of homosexual patients who believed or feared they had AIDS, to our knowledge there have been no reports of the delusion of having AIDS as a manifestation of an affective disorder in an individual who is not a member of a high-risk group. The purpose of this communication is to report our experience with several patients who, as a result of severe affective disorder, had the delusion that they had AIDS. The following cases are representative of our experience.

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CASE REPORTS

Case 1. Mr. A, a 53-year-old married white man, presented to the medical clinic of a large medical center with the complaint that he had been feeling tired and weak for the past several months. While he initially denied other symptoms during a review of systems, he confided to the physician during the physical examination that he had AIDS and that this accounted for his weakness and tiredness. Closer questioning of Mr. A revealed that he had never taken street drugs, had never had homosexual contact, and had not had blood transfusions.

Results of the physical examination and routine blood work were entirely within normal limits. When Mr. A was told of the normal results, he became angry and agitated and demanded "to have a blood test for AIDS." Attempts at calming and explaining to Mr. A were unsuccessful, and psychiatric consultation was requested.

During the mental status examination Mr. A was agitated and talking constantly of having AIDS. He noted that he had had one heterosexual contact outside the marriage and that this had occurred more than 20 years earlier. However, he believed that he had contracted the AIDS virus during that encounter and that the symptoms of the illness were now becoming manifest. Mr. A described an "unusual" sensation in his genitals and believed that he would die soon. He was so focused on the idea of having AIDS that it was only with great difficulty that he would respond to other questions. It was established that he had had early morning awakening, weight loss, and vague suicidal thoughts, but he denied being depressed in mood. Mr. A was admitted to the psychiatry inpatient service.

There was great difficulty in caring for Mr. A while he was on the inpatient unit. He would literally grab the physician at every opportunity to ask if it had been established that he had AIDS. Attempts to explain to him that AIDS testing would not be done, since he had no signs or symptoms of the illness, were futile. Mr. A's family, not realizing the delusional nature of his condition, also insisted that AIDS testing be done; the family believed that a negative result would alleviate all of Mr. A's concerns.

A complicating factor was the medical center's policy in regard to AIDS testing. The governing body of the facility had determined that routine testing would not be done, even on the higher-risk patients who had no signs or symptoms of the illness. Testing would only be done on those individuals with physical findings, and those findings would be validated by the infectious disease service. Because the infectious disease service was the only service that could order AIDS testing in the medical center, its staff were asked to consult on Mr. A's case. They agreed that Mr. A did not have AIDS, nor

did he need antibody testing; their attempts to explain this to the patient and his family were futile.

The *DSM-III-R* diagnosis made was major depression, single episode, with mood-congruent psychotic features. Mr. A was treated with an antidepressant medication, and, when he failed to respond, he was given ECT. After seven treatments he began to sleep and gain weight, and, more importantly, the delusion of having AIDS began to clear. When he was discharged, the delusion had completely cleared, and he was able to verbalize his guilt over the extramarital encounter years earlier.

Case 2. Mr. B, a 56-year-old married white man, was admitted to the psychiatry service of a medical center upon his transfer from a community hospital. The history revealed that he had been in his usual state of good health until some 4 months earlier, when he became apathetic, lost interest in his usual activities, quit his job, and stayed at home. He admitted to feeling depressed and having early morning awakening, weight loss, and crying spells but denied suicidal ideation. He had attempted to understand why he was feeling so badly and had been watching television many hours a day after quitting his job. He happened to watch a television show about AIDS, and it suddenly occurred to him that he had AIDS and that this explained why he was feeling as he was.

Mr. B had no history of drug use or abuse, nor had he ever had homosexual experiences. He had had heterosexual intercourse with numerous individuals before marriage but no extramarital sexual contacts since his marriage some 15 years earlier. A *DSM-III-R* diagnosis of major depression, single episode, with mood-congruent psychotic features, was made. Because Mr. B had been receiving therapeutic levels of antidepressant medication at the referring hospital without any observable improvement, it was decided to treat his depression with ECT. He responded to the treatments, and the delusion of AIDS vanished completely. The patient was in good spirits and considered completely recovered at the time of discharge.

Case 3. Mr. C, a 35-year-old single black man, presented with a chief complaint of having AIDS. He was brought to the admitting area of an inpatient psychiatric facility by family members. The family members reported that Mr. C had been loud, boisterous, threatening, and agitated since attending the funeral of a friend 5 days before admission. He subsequently created a disturbance in a local general hospital emergency room, demanding that he be tested and treated for AIDS.

The patient had a 15-year history of intermittent episodes of psychosis characterized by euphoria, hyperactivity, and grandiosity. He had experienced long periods of remission of up to 8 years while taking lithium carbonate. His functioning during remission was characterized by appropriate and satisfying social functioning. The patient had a single long-term heterosexual relationship and denied homosexual activity. He had never had blood transfusions or contact with blood products.

On admission, Mr. C was noted to be boisterous, aggressive, and demanding. A *DSM-III-R* diagnosis of bipolar disorder, manic, was made. Although he would not allow determination of serum lithium levels, recent noncompliance was suspected by family members. The patient began therapy with lithium carbonate and occasional doses of neuroleptics. In addition, seclusion was used when his behavior became extreme.

After 7 days of treatment, Mr. C became more compliant and allowed blood to be drawn for determination of serum lithium levels. This and subsequent serum lithium levels were all in the vicinity of 1.0 meq/liter. In the second week of hospitalization he began to regain his baseline level of activity, and other manic symptoms gradually resolved.

Mr. C was able to talk about the friend who had died. He reminisced about their long friendship and showed signs of normal grieving. After resolution of the psychosis, he never again brought up the question of having AIDS. When asked about having AIDS at the time of discharge, he stated that the possibility had never occurred to him. He stated that he rarely recalled the specifics of his behavior or ideational content during the psychotic episodes. In other words, he was unable to remember that he had believed he was afflicted with AIDS. The delusion and its memory had apparently disappeared with the psychosis.

Mr. C remained euthymic for 2 months after discharge. After 2 months, he again developed a manic episode requiring hospitalization. The delusion of having AIDS did not recur. Otherwise, diagnosis, treatment, and recovery followed a course similar to that in the prior hospitalization.

DISCUSSION

These cases are representative of our experience. We are aware of several other cases through colleagues. It should be noted that these patients were not members of what are generally considered groups at high risk for the development of AIDS or AIDS-related complex. Furthermore, they lacked physical disease manifestations often associated with AIDS, such as lymphoadenopathy, Pneumocystis carinii infection, or Kaposi's sarcoma. In each case, the belief that AIDS had been contracted disappeared when the patient was successfully treated for affective disorder.

Early scientific reports (4–6) and subsequent information disseminated to the public through news media suggest that the AIDS syndrome is insidious and fatal. Furthermore, the high-risk groups tend to be stigmatized (7), adding to the sense of enigma, if not evil. Subsequently, the very concept of having AIDS becomes an ideal delusion for a patient whose sense of guilt seeks a rational and tangible form. If sexual indiscretion is the dynamic source of guilt being magnified by affective disorder, AIDS provides both sexual motif and punishment. Indeed, the concept of AIDS as retribution for an immoral lifestyle has been identified as a common theme in patients who actually have the disease (8).

Some patients may demand to be tested for AIDS. There are guidelines (9) by which most clinicians abide as to who should be tested for the disease. In addition, a number of problems have been delineated that may arise simply as a result of testing for AIDS (10). The possibility that a patient's demand for AIDS testing may be based on the presence of a delusion adds another consideration to the ongoing controversy over AIDS testing. Some clinicians would provide such testing and offer negative results to the patient and family as part of the treatment. In our experience, this may be

helpful in demonstrating the nature of a delusion to the family. The patient, however, usually finds a way to negate the test results and continues to harbor the delusion until successfully treated for the underlying psychiatric disorder.

These cases illustrate that as the AIDS epidemic becomes a fixture in the public consciousness, it may become increasingly incorporated into the delusional material of patients with psychiatric disorders. We think it important that physicians become aware that patients without evidence of compromised immune status and without membership in high-risk groups may present with a complaint of having AIDS. Such a presentation should raise the physician's index of suspicion of an underlying delusional disorder. In such instances, the clinician should look for other signs and symptoms that might be helpful in making the appropriate psychiatric diagnosis (11).

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Twenty-Four-Hour Profiles of Body Temperature and Plasma TSH in Bipolar Patients During Depression and During Remission and in Normal Control Subjects

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The 24-hour patterns of body temperature and plasma thyrotropin (TSH) were measured in eight bipolar patients in both depressed and recovered (after 3 weeks of treatment) states and in eight normal control subjects. Clear circadian patterns were detected for both temperature and TSH. Nocturnal body temperature was increased and the nocturnal surge of TSH was blunted during depression; these abnormalities were corrected after recovery. The inverse relationship between changes in body temperature and TSH levels at night suggests that changes in thermoregulation may be responsible for the neuroendocrine disturbance and may play a role in the pathophysiology of depression.
(Am J Psychiatry 1988; 145:1133–1137)

The symptoms of thyroid disease strongly suggest that thyroid function and affective disorder are related. In the last decade, this association between thyroid hormones and mood has led investigators to search for abnormalities of thyroid function in primary affective disorders (1, 2). A blunted response of plasma thyrotropin (TSH) to infusion of thyrotropin-releasing hormone has been reported to occur in depression (3), but no consistent abnormalities have so far been found in levels of thyroid hormones in patients with depression. Secretion of the pituitary hormone TSH exhibits a circadian rhythm that peaks during the night (4, 5). Several investigators have reported abnormalities of this rhythm in endogenous depression, with reduction of its amplitude (6, 7) linked to a blunted nocturnal surge of TSH (8), which returned to normal in the remitted state (9–11).

Through their capacity to stimulate heat production, thyroid hormones play an important role in the regulation of body temperature in warm-blooded animals (12). Slight variations in body temperature related to changes in ambient temperature have been found to affect the thyroid axis: exposure to cold stimulates TSH secretion (13, 14), whereas exposure to heat inhibits TSH secretion (15, 16). In light of the relationship between TSH and body temperature, it is possible that an increase in body temperature at night could be responsible for the blunting of nocturnal TSH secretion which is observed in depression. In this regard, it is of interest that body temperature has been reported to be abnormally high at night in depressed patients (17–19). The purpose of this study was to measure the circadian rhythms of TSH and temperature simultaneously in the same subjects in order to determine whether blunted nocturnal secretion of TSH in depression might be related to an abnormality in the regulation of body temperature.

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METHOD

The investigation took place at the Psychiatric Clinical Center of Nice University in France. One group of subjects was composed of eight psychiatric inpatients (six female and 2 male; mean±SD age=52.8±7.4 years) with major depression according to *DSM-III* criteria. All of these patients had bipolar I illness and had previously been treated for both manic and depressive episodes. They were tested during a depressive episode and during remission. The second group consisted of eight normal subjects, sex- and age-matched to the patients, who had no medical complaints or history of psychiatric illness. A structured interview for diagnosis of affective disorders, schizophrenia, and dementia was conducted with each patient by at least two psychiatrists. The level of depression in each patient and each control subject was assessed with the 17-item Hamilton Rating Scale for Depression by a psychiatrist blind to the patient's diagnosis and treatment status. The reliability of both diagnosis and ratings was assessed by comparisons with those of other psychiatrists for larger patient populations. The subjects were all physically healthy, as confirmed by clin-

ical examination and blood tests. The patients participated voluntarily, and all the subjects were informed of the purpose of the study before their written consent was obtained.

The investigations took place after an initial 2-week period of drug withdrawal for the patients when they were in the depressed state and for the control subjects and after the third week of treatment with antidepressant medications (imipramine, N=3; amitriptyline, N=5), when the patients' depression had remitted. The study was carried out during the spring. The biological observations took place in a psychiatric ward under the following conditions. Patients and control subjects remained in bed for 25 hours, on a 14:10 light-dark cycle (more than 1500 lux for 14 hours and less than 50 lux for 10 hours) with constant ambient temperature (20 °C) and humidity. The patients and control subjects were asked to get up as little as possible and to remain in bed at least 20 minutes before each sampling. Standard hospital meals were served at 7:30 a.m., noon, and 7:00 p.m.

Blood samples (5 ml) for the estimation of TSH circadian rhythms were drawn hourly over 25 hours through an indwelling catheter that was placed in an antecubital vein at least 2 hours before the first sample was drawn. The blood samples were immediately centrifuged at 4 °C, and the plasma was stored at −20 °C for assays. Plasma levels were determined by radioimmunoassay. Body temperature was recorded continuously over the 25-hour period by means of a rectal probe.

The data analysis was based on three different methods. 1) Data for each hour were averaged for the subjects within a group (the patients when depressed, the patients when recovered, and the control subjects). 2) The 24-hour mean as well as the means when the subjects were awake (7:00 to 22:00) and asleep (23:00 to 6:00) were calculated for each group. 3) A cosine function was fitted to the data by using the least squares method (20): $f(t)=M+A\cos(wt+P)$, where $f(t)$ is the estimated value of the periodical function at time t, M is the mean level of the cosine function best fitting the data, A is its amplitude, w is its angular frequency, and P is the acrophase (time of the maximum). The minimum of the temperature rhythm and the maximum of the TSH rhythm were defined as the time of day (in hours and minutes) of the main trough and peak of the fitted functions. Data were expressed as the mean±SD of the individual values. Paired t tests were used to compare the patients in the depressed and remitted states, and unpaired t tests were used to compare the patients (when depressed and when recovered) with the control subjects. In addition, a two-way analysis of variance (ANOVA) for repeated measures was used to compare the circadian profiles of the patients during depression and after recovery. Pearson coefficients of correlation were used to analyze the relationship between clinical improvement (defined as the variation in Hamilton depression scores) and rhythm parameters.

RESULTS

The 24-hour and the awake mean levels of TSH did not differ among the groups of patients when depressed, patients when recovered, and control subjects (see table 1). However, the asleep mean level was lower in the patients during depression than during remission and lower in the patients when depressed than in the control subjects. The mean levels of the patients after recovery were not significantly different from those of the control subjects. The amplitude of the TSH rhythm was less in the patients during depression than during remission and less in the patients during depression than in the control subjects. The peak time position was slightly but not significantly advanced in the patients during depression compared with the peak of the patients in the recovered state and the peak of the control subjects. We found a significant interaction between mood state (depression versus remission) and the 24-hour variations of plasma TSH levels ($F=5.498$, $df=23$, $p<0.00001$).

The 24-hour mean body temperatures were similar among the groups. However, the awake mean temperature was lower in the patients during depression than during remission and in the patients in the depressed state than in the normal control subjects. The asleep mean temperature was higher for the patients during depression than during remission and for the patients when depressed than for the normal control subjects. The amplitude of the circadian temperature rhythm was also less in the patients during depression than during remission and less in the patients when depressed than in the control subjects. We failed to detect any significant phase disturbance of the temperature rhythm in the patients when they were depressed. We found a significant interaction between mood state (depressed versus recovered) and the 24-hour variations of body temperature levels ($F=5.707$, $df=23$, $p<0.00001$). These changes are evident in figure 1 for TSH and temperature in the patients when depressed and when recovered. As can be seen in figure 1, the more pronounced and significant (according to the two-way ANOVA for repeated measures) abnormalities occurred during the sleep period.

The decrease of patients' nocturnal body temperature levels after clinical improvement was negatively correlated with the increase of their nocturnal TSH levels ($r=-0.70$, $df=7$, $p<0.05$). Similarly, clinical improvement was negatively correlated with the decrease of the nocturnal body temperature ($r=-0.77$, $df=7$, $p<0.02$) and positively, but not significantly, correlated with the nocturnal increase of TSH ($r=0.49$, $df=7$, $p>0.05$).

DISCUSSION

To our knowledge, this is the first report of a relationship between changes in nocturnal TSH secretion and body temperature in the same patients observed

TABLE 1. Circadian Variation in TSH and Body Temperature in Bipolar Patients During Depression and After Recovery and in Control Subjects

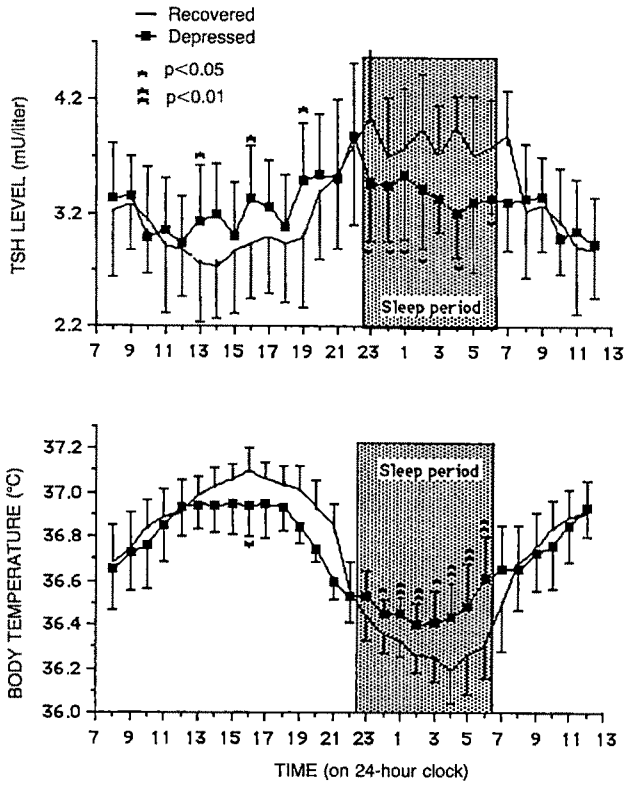
	Patients (N=8)				Control Subjects (N=8)		Depressed Versus Recovered (paired t test)		Depressed Versus Control (unpaired t test)		Recovered Versus Control (unpaired t test)	
	Depressed		Recovered									
Measure	Mean	SD	Mean	SD	Mean	SD	t (df=7)	p	t (df=14)	p	t (df=14)	p
Hamilton depression score	24.4	3.8	9.6	4.9	6.1	3.5	6.240	<0.001	5.291	<0.001	1.521	n.s.
TSH												
Plasma level (mU/liter)												
24-hour	3.31	0.29	3.38	0.28	3.41	0.27	0.964	n.s.	0.326	n.s.	0.127	n.s.
Awake	3.27	0.22	3.09	0.30	3.13	0.29	1.892	n.s.	0.425	n.s.	0.062	n.s.
Asleep	3.43	0.32	3.84	0.31	4.09	0.36	3.546	<0.01	2.425	0.03	0.850	n.s.
Amplitude	0.72	0.36	1.34	0.72	1.39	0.64	3.340	<0.02	2.142	<0.05	0.136	n.s.
Phase peak (mean= 24-hour clock time)	23:32	4 hr, 13 min	1:27	5 hr, 9 min	1:53	2 hr, 0 min	0.941	n.s.	0.998	n.s.	0.071	n.s.
Body temperature												
Temperature (°C)												
24-hour	36.69	0.12	36.69	0.14	36.73	0.13	0.050	n.s.	0.356	n.s.	0.410	n.s.
Awake	36.73	0.12	36.91	0.10	37.01	0.12	3.648	<0.01	3.017	<0.01	1.991	n.s.
Asleep	36.45	0.07	36.30	0.06	36.34	0.05	5.807	<0.001	2.289	<0.05	0.018	n.s.
Amplitude	0.24	0.13	0.39	0.10	0.44	0.08	4.536	0.003	3.323	0.005	0.980	n.s.
Phase trough (mean= 24-hour clock time)	2:05	2 hr, 15 min	3:53	2 hr, 10 min	4:26	2 hr, 4 min	1.223	n.s.	1.421	n.s.	0.699	n.s.

during clinical depression and during remission. In contrast to the control subjects, the depressed bipolar patients had reduced nocturnal TSH secretion and increased nocturnal body temperature. These two abnormal conditions returned to normal after recovery. Our findings with respect to TSH are consistent with those in previous studies by Weeke and Weeke (6, 7), who reported diminished nocturnal TSH secretion in a mixed sample of depressed patients—findings since confirmed by other investigators (8, 10, 21). The increase in nocturnal TSH level observed after recovery is also consistent with other findings (9, 10) and with findings in our previous study of patients with endogenous depression (11). As far as body temperature is concerned, our finding of a reduced amplitude in temperature rhythm in depression is consistent with the results of most previous studies (17–19, 22–24). Similarly, nocturnal body temperature has been reported to increase in depressed patients and then return to normal during remission (25). TSH and body temperature rhythms were slightly phase advanced in our patients when they were depressed compared with when they were in remission and compared with the control subjects. However, consistent with previous reports (19, 23, 26), this difference was not statistically significant, possibly because the sample was small. The increased body temperature observed during the day in our patients during remission may have been related to the increased motor activity reported to occur in remission (26).

Our findings of an inverse relationship between TSH secretion and body temperature in bipolar patients is also consistent with the results of a study by O'Malley et al. (16), which showed decreased secretion of TSH and increased body temperature during the night in normal subjects exposed to heat; these patterns resemble those observed in depression. These findings suggest that thermoregulation may be impaired in depression. In this regard, treatments of depression have been shown to affect thermoregulatory functions: antidepressant drugs such as amitriptyline have been reported to reduce body temperature in animals, normal subjects, and depressed patients (17, 24, 27) and to decrease the resting metabolic rate in depressed patients (28). This effect of tricyclics on body temperature may thus account for the reported increase in TSH levels after treatment (29, 30). Similarly, a drop in resting core temperature (31) and an increase in nocturnal TSH level (21) have been noted during sleep deprivation in humans. Moreover, elimination of REM sleep, which has an antidepressant effect (32), presumably further reduces the thermal load on the brain by preventing the elevation of brain temperature that normally occurs during REM sleep (33).

In mammals, thermoregulation is impaired during sleep (especially REM sleep) (34) and undergoes circa-

FIGURE 1. Mean±SD 30-Hour (Extended 24-Hour) Profiles of Plasma TSH and Body Temperature in Eight Bipolar Patients During Depression and After Recovery[a]



[a]p values indicate significant differences between the means of the patients and the control subjects.

dian variations in such a way that it is less effective at night (35). This circadian variation of thermoregulatory processes may explain why temperature and related TSH abnormalities are more pronounced at night in depression. The hypothesis of impaired thermoregulation in depression receives additional support from the observation that patients with a seasonal form of affective disorder that appears to be sensitive to environmental temperature become depressed during hot weather and improve during cold weather (36). Future studies are needed to evaluate the clinical and endocrinologic effects of body temperature manipulations in depressed patients.

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Placebo Response in Panic Disorder

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Of 43 patients with panic disorder or agoraphobia with panic attacks who took placebo for 8 weeks in two double-blind studies, one in four markedly improved. Those with consistently normal dexamethasone suppression test results were significantly more likely to show a placebo response as were those with lower anxiety ratings at the outset of treatment.

(Am J Psychiatry 1988; 145:1138–1140)

The decision to use medication, whatever the illness, rests on the expected balance between adverse and beneficial results. These expectations are based on the clinician's experience and the relevant literature, both of which rely on contrasts between patients who have done well with that treatment and those who have not; however, these contrasts also reflect to unknown degrees natural history and placebo response. Attempts to identify specific features associated with maximum differences between drug and placebo outcome (true drug effects) are rare since they require larger samples than those needed simply to compare drug and placebo outcomes. The prediction of placebo response per se constitutes a simpler, more accessible design, yet such studies are likewise infrequent (1).

Most of the placebo response studies in psychiatry have described depressed patients. The more recent of these, studies using operational criteria for diagnostic subtypes, have found placebo response more likely among patients with nonendogenous, nonmelancholic, or nonpsychotic major depression (1–3). More resistant to placebo are patients with longer illness durations, with greater severity, with co-morbidity (1, 4), and with abnormal responses to dexamethasone (5, 6).

The pharmacotherapy of anxiety disorders likewise involves substantial placebo effects and many controlled trials have, in fact, failed to show the superiority of active drug over placebo (7). However, almost no data exist to separate anxiety disorder patients who are more sensitive to placebo from those who are less so. One study found that patients with phobic anxiety were more likely to respond to placebo if they did not experience panic attacks (8); several others found that patients with panic disorder rarely respond to 1 or 2 weeks of placebo alone (9–11). Only Ballenger et al. (11) have described panic disorder patients given placebo alone for an extended period, and in that series placebo response was common; by week 4, 43% had achieved at least "moderate improvement."

The drawbacks of pharmacotherapy for panic disorder are well-known. A variety of side effects attend the use of tricyclic antidepressants and monoamine oxidase inhibitors, and benzodiazepines are often difficult to discontinue. It is worthwhile, then, to determine whether placebo response is likely among panic disorder patients in general and, if so, whether certain demographic or clinical features predict such responses.

METHOD

The data arose from two sequentially executed studies of panic disorder: One compared alprazolam and placebo, and the other compared alprazolam, diazepam, and placebo. These were sponsored by the Upjohn Company, and the University of Iowa was one of a number of participating centers; we describe only data collected at Iowa. Both studies used random assignment after at least 1 drug-free week, were conducted under double-blind conditions, and included 8 weeks of active drug or placebo treatment.

Patients were recruited from the University of Iowa outpatient clinics or through newspaper advertisements. All subjects met *DSM-III* criteria for panic disorder or agoraphobia with panic attacks, and all had experienced at least weekly panic attacks during the preceding 3 weeks. All subjects provided informed consent. Excluded were patients with bipolar illness, melancholia, alcoholism active in the previous 6 months, psychotic disorders, or major depression that predated or clinically predominated the panic disorder.

A 1-week drug-free period preceded random assignment to treatment. Patients who had been taking the equivalent of 20 mg or more each day of diazepam were tapered gradually from medication beforehand. Capsules in the first study contained placebo or 1 mg of alprazolam; the second study introduced a third cell and some capsules contained 10 mg of diazepam.

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Doses were increased during the first 3 weeks to six capsules per day, if tolerated; subsequent increases to 10 capsules per day were then possible depending on clinical response. We describe only the patients who took placebo.

Participating psychiatrists determined diagnoses using the Structured Clinical Interview for *DSM-III* Diagnosis—Upjohn version (12). Baseline severity measures, repeated during treatment, included the Hamilton Rating Scale for Depression (13) and the Hamilton Rating Scale for Anxiety (14). Physicians made global judgments of change during treatment on an 11-point scale on which 10 signified total recovery, 5 a lack of change, and 0 marked worsening. For this report, "marked improvement" corresponds to ratings of 8, 9, or 10 on this scale.

These measures were used to reevaluate patients after 1, 2, 3, 4, 6, and 8 weeks of therapy. Outside of the brief supportive therapy routinely accompanying pharmacotherapy, patients received no other treatment interventions. Specifically, patients were not involved in group therapy or behavioral therapy, nor were they urged to confront phobic situations when such existed.

Patients were instructed to take 1 mg of dexamethasone on the evening before the visit ending the 1-week drug-free period. A single sample for plasma cortisol measurement was drawn during the visit, typically in the afternoon. This procedure was repeated after 3 and 8 weeks of treatment. Patients who did not meet the exclusion criteria listed by Carroll et al. (15) were not tested in this way. Cortisol was measured by using a radioimmunoassay with a specific cortisol antiserum obtained from Damon Diagnostics, Needham Heights, Mass. This antiserum showed no cross-reactivity with dexamethasone, progesterone, testosterone, or 11-deoxycortisol. Intra- and interassay coefficients of variation were 12.2% and 11.1%, respectively, for the first cohort, and 9.7% and 11.7%, respectively, for the second cohort. An earlier report (16) described dexamethasone suppression test (DST) results for the first cohort and used a postdexamethasone cortisol level greater than 4 μg/dl to define nonsuppression (on the basis of results in 23 normal control subjects). This analysis adopts the same threshold.

RESULTS

Of the 50 patients who entered the study and completed a baseline DST, three failed to complete the first 3 weeks of placebo therapy, and a total of seven (14.0%) had dropped out by the end of the trial. None of these seven patients had been globally rated as recovered when last seen.

Of the 47 patients who completed 3 weeks of placebo therapy, seven (14.9%) markedly improved, and only 25 (53.2%) failed to improve to at least some extent. After 8 weeks, 11 (25.6%) of 43 remaining patients had markedly improved, and only 26 (60.5%) were unchanged or worse relative to their baseline condition. By weeks 3 and 8, respectively, 11 (23.4%) of 47 and 12 (27.9%) of 43 patients had experienced a reduction of 50% or greater from their baseline Hamilton anxiety scale scores.

Only two of the patients who completed the protocol were rated globally as markedly improved after 1 week of placebo, and subsequent ratings consistently indicated that both remained markedly improved. Marked improvement in other patients was considerably less stable, however; of five patients so rated at week 2 of placebo, four (80.0%) received at least one later rating of "not markedly improved."

Patients who had markedly improved at week 3 had significantly lower Hamilton anxiety scores at baseline and somewhat lower postdexamethasone cortisol values (table 1). Only the number of panic attacks during the baseline week significantly predicted marked improvement at 8 weeks, although substantial trends suggested that lower anxiety scores and lower postdexamethasone cortisol levels predicted placebo response at week 8 as well. Of note, only one (7.7%) of the 13 baseline nonsuppressors had responded to placebo by 8 weeks, compared to 10 (33.3%) of the 30 baseline suppressors. Neither Hamilton anxiety scale scores nor postdexamethasone values at baseline predicted clinical conditions at week 8 as measured by Hamilton anxiety scale scores, Hamilton depression scale scores, or total numbers of panic attacks.

Six patients who suppressed normally at the baseline assessment became nonsuppressors after 3 weeks of placebo; 5 weeks later, only one (16.7%) of these patients was considered even minimally improved from their condition at baseline.Thus, the absence of abnormal DST results was significantly associated with a likelihood of eventual placebo response. Of 16 patients with normal DST results both at baseline and week 3, seven (43.8%) were markedly improved by 8 weeks, compared to only two (10.5%) of the 19 patients who were nonsuppressors at either baseline or week 3 ($p=0.03$, Fisher's exact test).

Placebo responders were roughly one-half as likely as nonresponders to have begun the study with a major depression. There was no significant relationship between baseline postdexamethasone cortisol levels and current depression, however; five (38.5%) of the 13 depressed patients and nine (24.3%) of the 37 nondepressed patients were nonsuppressors. Moreover, the relationship between DST results and outcome remained when these 13 patients were removed from that analysis. Of the 16 nondepressed patients with normal DST results at both baseline and week 3 evaluations, seven (43.7%) were markedly improved by week 8; only one (16.7%) of the six nondepressed patients with abnormal DST results was markedly improved by week 8.

Although patients with two normal DST results had relatively high recovery rates with placebo, recovery rates with active drug treatment were substantially higher still. In a separate report (17), we described the patients given alprazolam in this protocol. We found

TABLE 1. Baseline Characteristics of Patients With Panic Disorder Who Did or Did Not Improve After 3 and/or 8 Weeks of Placebo Therapy

Rating of Markedly Improved	Women (%)	Age (years)		Current Major Depression		Work/Social Disability Rating		Hamilton Anxiety Score		Baseline Week Panic Attacks		Hamilton Depression Score		Postdexamethasone Cortisol Level (μg/dl)		Postdexamethasone Cortisol >4 μg/dl			
																		At Baseline or Week 3[a]	
		Mean	SD	N	%	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	N	%	N	%
At 3 weeks																			
No (N=40)	72.5	36.4	9.3	12	30.0	3.8	0.9	22.0	7.3	9.7	11.7	17.8	5.9	4.0	3.3	13	32.5	0	—
Yes (N=7)	57.1	40.0	7.9	1	14.3	3.7	1.0	15.0[b]	6.6	2.4	1.6	14.0	3.9	2.6	0.6	0	0.0	0	—
At 8 weeks																			
No (N=32)	75.0	36.4	9.5	11	34.4	3.7	0.9	21.0	7.6	9.1	9.8	17.6	5.8	4.2	2.9	12	37.5	17	65.4
Yes (N=11)	63.6	40.2	8.9	2	18.2	4.0	1.0	17.6	7.5	2.9[c]	2.2	15.1	5.5	3.4	3.7	1	9.1	2	22.2[d]

[a]Excludes patients whose DST results were normal at baseline and missing at week 3 of placebo therapy.
[b]Significant difference between those who markedly improved and those who did not after 3 weeks of placebo (t=2.23, df=45, p=0.02).
[c]Significant difference between those who markedly improved and those who did not after 8 weeks of placebo (t=3.4, df=41, p=0.002).
[d]Significant difference between those who markedly improved (N=9) and those who did not (N=26) after 8 weeks of placebo (p=0.03, Fisher's exact test).

that 42 (80.7%) of the 52 patients given alprazolam who completed the study had final global ratings of 8, 9, or 10, and their baseline DST results were not related to the likelihood of recovery. Thus, although the differences in outcome between placebo and active drug are particularly marked for nonsuppressors, they are also significant for suppressors.

DISCUSSION

Factors that predict lack of placebo response in depressed patients—the presence of melancholic, endogenous, or psychotic features, longer duration, complicating illnesses, and abnormal DST results—have in common a general association with severity of illness. Likewise, the more severely affected anxiety disorder patients, those with panic attacks, are relatively resistant to placebo. In turn, patients with panic attacks are even less likely to improve with placebo if they abnormally suppress cortisol after dexamethasone administration.

Panic disorder patients are often hesitant to take medication, particularly after experiencing early side effects. The odds of a spontaneous remission or placebo response should be inversely related to the vigor with which pharmacotherapy is recommended, and in this light, factors predictive of recovery without drugs have practical implications.

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A Study of Filicidal Men

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Twelve filicidal men were examined on a forensic psychiatric service. The majority suffered from severe mental impairments due to psychosis, neurological disorders, substance abuse, or mental retardation. Most of the filicidal acts committed by these chronically impaired men resulted from isolated explosive behavior.
(Am J Psychiatry 1988; 145:1141–1144)

Filicide is the killing of a child by his or her parent. About 3% of American homicides are filicides (1). The world literature (2, 3) indicates that mothers commit far more filicides than fathers. Maternal infanticide and filicide have been investigated extensively, but paternal filicide has not. This paper, a continuation of earlier studies of family murder (4, 5), will present data on 11 cases of parental filicide and one case of attempted filicide.

METHOD

We reviewed hospital records and identified 12 men charged with filicidal acts who were examined at the Bellevue Hospital Forensic Psychiatry Unit from 1970 to 1982. Since 1979 inmates have been diagnosed according to *DSM-III* criteria. Inmates examined earlier were rediagnosed for this study with *DSM-III* criteria by means of chart review. All inmates received routine laboratory workups and physical and neurological examinations. All 12 men were seen by one of us (J.M.C.) for psychological evaluation.

Demographic data on these 12 men are presented in table 1. They were examined with the goals of deriving a better understanding of paternal filicide and of identifying familial, developmental, and psychological features characteristic of filicidal men. The following case vignettes present the common psychological and social factors.

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CASE REPORTS

Case 1. Mr. A adopted his wife's 11- and 13-year-old daughters and 10-year-old son. He was a chronic alcoholic with a history of alcohol withdrawal delirium, and he continued to drink daily. His memory of the murder was deficient, but he recalled hearing disparaging and accusatory auditory hallucinations before the killing and having visual hallucinations and formication several days thereafter. He was delusional on the night of the murder, believing that his wife was unfaithful. He choked and stabbed her and attacked the three children. The boy was stabbed to death.

In custody Mr. A attempted suicide. Neurological and psychological testing, however, revealed no psychotic or organic mental disorder symptoms. His diagnoses were organic delusional syndrome and alcohol hallucinosis.

Case 2. Mr. B required psychiatric hospitalization and residential treatment throughout childhood and adolescence. His mother was hospitalized for psychosis, two brothers died violently, and a sister committed suicide. As an adult Mr. B was also hospitalized for recurrent psychotic episodes. He was also jailed for larceny, assault, and selling and using drugs. He lived with his common-law wife, who was 8 months pregnant with his child, and his stepson.

Mr. B suffered persecutory delusions for several months before he murdered his family, and he acknowledged using marijuana, alcohol, heroin, and other, unknown substances during that time. After wandering the streets for a few weeks, he became convinced that his wife (soon to give birth), his stepson, and his dog were all evil and conspiring to destroy him. He strangled them all in an explosive rage. After he was apprehended he continued to have delusions and a formal thought disorder. His diagnoses were paranoid schizophrenia, polysubstance abuse, and intoxication.

Case 3. As a child Mr. C was physically abused by his father and assaulted his own stepmother. He was placed in foster care and at age 11 was institutionalized as mentally retarded. He was released to the street at age 15 and survived by begging and stealing. He attempted suicide once and was hospitalized several times for depression. He married at age 19 and fathered two children. After he and his wife separated she abandoned the children, so he brought them to live with him and an older woman to avoid their placement in foster care.

Police were called to investigate the reportedly accidental drowning of Mr. C's 5-year-old daughter. Mr. C confessed that he had drowned her with scalding water. While in custody he attempted suicide. Neuropsychological testing revealed depression and "diffuse organic impairment." He was found to have an IQ of 44. His diagnoses were moderate mental retardation, organic personality syndrome, and major depression-recurrent.

TABLE 1. Characteristics of 12 Men Charged With Filicidal Acts

Subject	Age (years)	Ethnicity	Religion	Education (years)	IQ	Occupation	Marital Status	Other Members of Household
1 (Mr. A)	36	Black	Protestant	9	97	Sales clerk in liquor store	Married	Wife, three children
2 (Mr. B)	35	Hispanic	Catholic	9	—	Unemployed	Common law	Wife, stepson
3 (Mr. C)	26	Hispanic	Catholic	3	44	Unemployed	Common law	Wife, two children
4 (Mr. D)	31	White	Protestant	10	83	Unemployed	Married	Wife, baby
5 (Mr. E)	17	Black	—	—	—	Unemployed	Separated	Sister
6 (Mr. F)	26	White	Catholic	12	123	Bank clerk	Married	Wife, her three children, their baby
7 (Mr. G)	40	Hispanic	Protestant	6	—	Unemployed	Common law	Wife, eight children
8 (Mr. H)	21	Hispanic	Catholic	11	—	Unemployed	Common law	Wife, two children
9	26	Hispanic	Catholic	10	49	Shipping clerk	Separated	Mother, sister, sister's family
10	34	Black	Protestant	6	—	Carpenter	Married	Wife, two children
11	29	Black	Protestant	—	—	Subway conductor	Married	Wife, baby
12	26	Hispanic	Catholic	6	—	Unemployed	Separated	Mother

Case 4. Mr. D required residential treatment and hospitalization from the age of 6 for epilepsy and conduct disorder. He was neglected and abused by his violent, alcoholic father and deaf mother. At age 15 he was institutionalized after trying to kill his father. He returned home at age 20 but again attempted patricide and was hospitalized.

Mr. D married at 22 and fathered two children but was divorced because of his depression and alcohol abuse. At age 30 he married a mentally deficient woman with polio and epilepsy, whom he physically abused. They had one daughter. Mr. D attempted suicide in reaction to his mother's death. Shortly after discharge from the hospital, while alone with his 3-month-old baby he beat her to death because he "couldn't stand her crying." A psychiatric examination revealed that he was impulsive but not psychotic. His IQ was 83. Skull films and an EEG were normal. His diagnoses were cerebral palsy, epilepsy, and organic personality syndrome, explosive type (*DSM-III-R*).

Case 5. Mr. E was placed in residential treatment at age 9 for violent behavior, and he continued to have conduct problems through childhood. By age 16 he was experiencing derogatory auditory hallucinations and grandiose and persecutory delusions. At that time he was abusing marijuana, cocaine, alcohol, and phencyclidine. While he was living with an older sister his girlfriend brought their 5-month-old child to visit. She implied that the baby was not his, and he interpreted this to mean that the baby was the devil. In a panic he threw the baby out of a fifth floor window, causing critical injuries. Mr. E was psychotic when admitted to Bellevue. He improved while taking antipsychotic medication, and no evidence of organic impairment was found. His diagnosis was phencyclidine-induced delusional disorder.

Case 6. Mr. F was raised by his promiscuous, alcoholic mother and by a strict aunt and uncle who physically abused him "in order to toughen him up." At age 8 he was homosexually abused and was subsequently bullied and ridiculed by peers. He avoided women and lived with his mother until age 25, when he married an older woman with three daughters. After a year he and his wife had a baby boy. He thought the baby would develop "sexual problems" like his, so he used rough play to "toughen him up." Once when he threw the baby into the air, the child's head hit the door frame, causing his death.

In custody Mr. F was bullied and threatened with rape. He became depressed and attempted suicide twice. His diagnoses were avoidant personality disorder and adjustment disorder with depressed mood.

Case 7. As a child Mr. G had developmental cognitive and learning problems and dropped out of the sixth grade. He entered a common-law relationship at age 26, producing eight children over 14 years. Other than his military service, he could not remember when he worked last. The family was on welfare. They were investigated twice for child abuse in the year preceding the filicide.

Mr. G's 13-month-old daughter died in the hospital. He was intoxicated when he brought her there. He said she had rolled off a bed. Autopsy revealed she had been beaten, burned, and starved, and she had numerous fractures. He and his wife were arrested. On examination his thinking was found to be delusional with bizarre features. His EEG was read as "suspicious." His diagnoses were chronic schizophrenia and alcohol dependence.

Case 8. Mr. H's mother was promiscuous. He saw her murdered when he was 5 years old. Subsequently his father was also murdered. Mr. H was raised in orphanages and foster homes, where, he claimed, he was beaten and raped. At 17 he was expelled from an orphanage for impregnating his 16-year-old girlfriend. Thereafter he abused drugs and alcohol and attempted suicide. He and his girlfriend reunited a year later and had another daughter. Their first daughter was then returned to them by the Bureau of Child Welfare. The family lived on intermittent welfare payments and what they could beg or borrow.

Mr. H's older daughter was developmentally delayed, which caused him grief and frustration. This reaction culminated in an explosive rage when the 3-year-old girl refused to eat her canned spaghetti (the only food in the house), making a mess of it. When Mr. H's wife returned home, he was amnestic and the child was battered to death. He tried burying her in a park, but the ground was frozen. He then surrendered to the police. No psychotic features were found during the examination. Mr. H claimed to have a history of significant head trauma but refused to have an EEG or neuropsychological tests. He denied substance abuse. His diagnosis was borderline personality disorder, possibly organic personality syndrome.

DISCUSSION

A European study published in 1967 (3) and a British report in 1973 (6) indicated that 25% of the homicides examined were filicides, while during the 1970s only 3% of U.S. homicides were filicides (1). Recent figures (7) show that homicides are increasing in England and that filicides now compose only 10% of that total. U.S. filicides remain at 2%–3% of all homicides and 29% of all child homicides (8). In a review of the world literature (2), a 44% prevalence of psychosis was found among filicidal fathers. A forensic pathology study of filicide (9) suggested that psychosis may be the most frequent precipitant among fathers. Other studies (3, 10, 11) have identified psychopathy, alcoholism, and isolated explosive disorders as factors in paternal filicide. A New York City police report (12) during our study period found that 24% of all New York City homicides were drug related and established that substantial numbers of the murder victims and offenders had consumed alcohol.

Several authors have speculated about motivations in filicide: mercy killing, killing out of hatred, impulsive psychotic behavior, chronic physical abuse, revenge against the spouse, elimination of unwanted children, and accidental death during sexual or sadistic abuse. Scott (6) reviewed several classifications and suggested one himself, but he pointed out that determining motivation is difficult and often speculative. He further stated, "[Filicidal fathers] commit the offence when their higher controls of discretion, reason . . . are in abeyance, . . . acting at so primitive a level that such sophisticated motives as revenge and altruism may be inappropriate . . . . Long continued states of indecision and stress [are] most likely to undermine defenses and to uncover [murder]." Scott presented material on 29 child killers, but most were not the biological fathers of the victims. These men were impulsive and had difficulties coping with stress. They also tended to misinterpret children's behavior as threatening, rejecting, or in some way provocative. No significant prevalence of mental illness was reported.

In this study of 12 filicidal men, a variety of specific factors were explored, and there were several developmental factors of note. Nine of the 12 men had significant neurological or psychiatric disorders of childhood. Several had been abused physically or sexually. Seven of the 12 had been separated from their families in childhood; four required residential treatment for aggressive behavior, and three had required placement because of maternal incompetence or death.

Frequent social factors in adulthood included poverty, social isolation, lack of familial or institutional social support, and an impulsive behavior style frequently involving substance abuse. In fact, substance abuse was a critical factor in most filicides in this study. Seven of the men were intoxicated, and all of these seven were psychotic, having either acute substance-induced psychoses or chronic psychoses exacerbated by alcoholism.

Neurological disorders were documented or suspected in half of this group. Three subjects were cognitively impaired (two and possibly all three were moderately mentally retarded), one was epileptic and had an organic impulse disorder, and one substance abuser suffered from blackouts, visual disturbances, and other neurological impairments. One man with a history of head trauma refused evaluation.

Psychiatric disorders were prevalent in this group. Eleven of the 12 had significant psychiatric disorders, ranging from the characterological to the psychotic. Seven men, all intoxicated, suffered from either acute or chronic psychoses.

There was no altruism, mercy killing, revenge against a spouse, or sexual motivation in these killings. When a motive could be elicited, it usually indicated parental misinterpretation of child behavior. Two men killed in fits of alcohol-induced jealousy. Three psychotic men killed their children because they believed the children were threatening them. Two cognitively impaired men "abused their children to death" over a period of time. Three men who had not been abusive previously killed their children in explosive rages at stressful times in their lives. Two sober, nonpsychotic men killed their children unintentionally during reckless endangerment.

Several conclusions may be drawn from these data. Most of the filicidal men grew up with multiple developmental stressors: exposure to violence, parental abuse, separation from parents, parental death. Most of the subjects had psychological or neurological problems that increased their vulnerability to abuse, neglect, and further developmental deviation. As adults, most lived in poverty and isolation from social supports.

As a group these men were not physically abusive until the killings. Only the cognitively impaired men had histories of chronic abuse. In contrast to physically abusive fathers, among whom psychosis is rare (13–15), at least nine of the 12 filicidal fathers had psychotic or organic impairments. Excluding the two cases of reckless endangerment, these filicidal fathers were severely mentally impaired. This group showed a greater prevalence of psychotic illness than previously noted in the literature. We conclude that organic impulse disorders, substance-induced disinhibition, and delusional or cognitive impairments of judgment all served to break the fragile sense of reality and impulse control in these men. This permitted the eruption of homicidal violence toward their children.

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The Relationship of Presenting Complaints to the Use of Psychiatric Services in a Low-Income Group

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The presenting complaints of 503 subjects who contacted a mental health clinic serving an inner-city, low-income group were classified into mental state, physical functioning, social relations, and social performance. The authors examined the relationship between type of presenting complaint and race ethnicity, gender, age, marital status, DSM-III *diagnosis, source of referral, and previous use of psychiatric services. Diagnostic group, source of referral, previous use of services, and type of presenting complaint were the four best predictors of number of outpatient visits. The increment in prediction produced by type of presenting complaint, however, was relatively modest.*

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Clinicians and administrators who provide outpatient mental health services are faced with large numbers of patients who have problems of living or social complaints, rather than complaints that may be appropriately called "medical" (i.e., psychiatric or physical symptoms). Presenting complaints reflect the strategies used by patients to seek the attention of the care givers (1–3). In conducting this research we had two objectives: 1) to determine the relationships of patients' presenting complaints to race ethnicity, gender, age, marital status, *DSM-III* diagnosis, source of referral, and previous use of services and 2) to measure the relative importance of presenting complaints to prediction of the use of outpatient psychiatric services.

Some important factors that have been shown to be related to the use of outpatient services are sociodemographic variables (particularly gender, race, and social class), psychiatric diagnosis, source of referral, and previous use of psychiatric services (4–6). These factors, however, have not been compared with the type of presenting complaint for their ability to predict the use of psychiatric services. The differences in needs and expectations related to race, ethnicity, and gender influence the ways in which services are used, but they are often overlooked in the course of outpatient treatment (7–9). However, to our knowledge no studies relating presenting complaints to the use of services have been conducted in a treatment setting organized and staffed to meet the special needs and expectations of low-income patients.

Furthermore, the existing studies relating presenting complaints to the use of psychiatric services have suffered from several methodological limitations. For example, some studies (10) have used the diagnostic criteria of *DSM-II* (less reliable) rather than *DSM-III* (more reliable). Other studies (11, 12) have used predefined lists for patients to indicate complaints, thus limiting or influencing the options available to patients to voice their difficulties. Some studies (11, 13) have examined groups with mixed incomes rather than primarily poor patients, who are at high risk for mental disorders. In a group with mixed incomes, poorer people compete with wealthier people for admission to services. This competition for services could distort the spontaneity of the complaints expressed by low-income people because of assumed or real preferential treatment of the people with higher incomes. As a result of these limitations, the relationship between patients' presenting complaints and their use of psychiatric services remains poorly documented. The research reported herein was aimed at overcoming these limitations by studying low-income patients in a clinic set up to meet their special needs. Its purpose was to refine and expand the existing knowledge on the role of presenting complaints in a low-income group.

METHOD

The subjects (N=503) were all individuals who contacted a university-affiliated outpatient psychiatric clinic for treatment during the 2-year period from July 1, 1981, through June 30, 1983. There were 199 male subjects (39.6%) and 304 female subjects (60.4%). The mean±SD age was 33.7±12.9 years. Blacks constituted 50.5% of the sample, Hispanics 25.6%, and whites 23.8%. The percentages of men in the three

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ethnic groups were as follows: blacks, 37.0%; Hispanics, 36.4%; and whites, 48.3%. Social class was determined with the Hollingshead two-factor index: 85% of the subjects were from class V (the lowest social class), and 15% were from class IV (14). The demographic characteristics of this sample were representative of the patients treated at the clinic: a low-income, inner-city group residing in a predefined catchment area.

Complaints were defined as the reasons stated by the subjects for seeking treatment when they first contacted the clinic. Each complaint was recorded verbatim by a trained, supervised clinician. The primary task of this clinician was to collect data from each subject who telephoned the clinic for an appointment or who walked in and requested an evaluation. When more than one complaint was voiced, only the complaint stated first was considered for analysis.

A comprehensive evaluation of each subject who kept his or her appointment was conducted by a team that included the clinician primarily responsible for the treatment of the subject, his or her supervisor, and a psychiatrist or psychiatric resident. After this evaluation, psychiatric diagnoses were assigned by the team according to *DSM-III* criteria. Patients with primary diagnoses of alcoholism or substance abuse were not admitted to the clinic; they were referred elsewhere.

Two researchers independently classified each complaint as one of four types of disturbance: mental state, physical functioning, social relations, and social performance. The first two areas of disturbance were considered medical complaints (i.e., symptoms); the last two were considered social complaints (i.e., problems of living). For example, hearing voices was regarded as a medical complaint in the area of mental state, and trouble with the law was regarded as a social complaint in the area of social performance. Two subjects simply stated, "I want to be admitted to the clinic." It was agreed that this statement would be rated as a complaint in the area of mental state. Some subjects (N=75) stated that they were seeking admission because they were told to do so by social agencies (e.g., the probation office). These statements were classified as complaints in the area of social performance. Agreement between the two raters on the classification of complaints by area of disturbance was achieved in one or two attempts.

The reliability of the complaints was studied by checking the complaints of a random sample of 50 subjects. On the day after the initial call was received, each subject was contacted by telephone and was again asked to give the reason for seeking treatment. In the case of a subject who had no telephone, the reliability of the complaint of the next subject who called the clinic for treatment and had a telephone was checked. The complaints noted when the subjects first contacted the clinic and those stated subsequently were found to be the same for 45 (90%) of the patients in the reliability group. The differing initial and subsequent complaints of the other five subjects were randomly presented to the raters, and each pair was independently classified by the raters as belonging to the same area of disturbance.

TABLE 1. Types of Presenting Complaints of 503 Subjects Who Did or Did Not Keep Initial Appointments at an Outpatient Psychiatric Clinic for Low-Income Patients

Type of Presenting Complaint	Kept Initial Appointment (N=382)		Did Not Keep Initial Appointment (N=121)	
	N	%	N	%
Mental state	179	46.9	53	43.8
Physical functioning	22	5.8	12	9.9
Social relations	97	25.4	26	21.5
Social performance	84	22.0	30	24.8

Chi-square tests and t tests were used to determine the statistical significance of the associations between the type of presenting complaint (mental state, physical functioning, social relations, and social performance) and each study variable. A stepwise regression was used to determine the relative importance of the type of presenting complaint in predicting the number of outpatient visits to the clinic. In the regression, the logarithm of the number of outpatient visits was used as the dependent variable to provide a better fit. Dummy variable coding was used to enter categorical variables. To enter the presenting complaint data, for example, three dichotomous group membership variables were used. The regression analysis employed was the maximum R^2 improvement technique (15). This stepwise regression technique finds the best one-variable model, the best two-variable model, and so forth until no switch can further increase the proportion of variance explained (i.e., R^2). After each new variable is entered, all possible switches are compared, and the one that produces the largest increase in the proportion of variance explained is made. This analysis was conducted both with and without the patients whose outpatient admissions eventually led to transfers to inpatient treatment.

RESULTS

A total of 61 different presenting complaints was compiled from the patients. Of these, 30 were in the area of mental state, seven in the area of physical functioning, nine in the area of social relations, and 15 in the area of social performance. The distribution of the patients who did and did not keep their initial appointments among the four types of complaints is shown in table 1. Of the 382 who were admitted for outpatient evaluation, 27 (7.1%) were eventually transferred to an inpatient psychiatric unit.

Table 2 shows the distribution of the subjects with the four types of complaints by the sociodemographic variables included in the analysis, *DSM-III* diagnoses, sources of referral, and use of psychiatric services. The

TABLE 2. Relationship of Presenting Complaint to Sociodemographic Variables, Diagnosis, Source of Referral, and Use of Psychiatric Services in an Outpatient Clinic for Low-Income Patients

		Medical Complaints						Social Complaints					
		Mental State		Physical Functioning		Any Medical Complaint		Social Relations		Social Performance		Any Social Complaint	
Variable[a]	N[b]	N	%	N	%	N	%	N	%	N	%	N	%
Race/ethnicity and gender[c]	503												
Whites													
Men	58	19	32.8	0	0.0	19	32.8	11	18.9	28	48.3	39	67.2
Women	62	28	45.2	3	4.8	31	50.0	18	29.0	13	20.9	31	50.0
Blacks													
Men	94	40	42.6	8	8.5	48	51.1	16	17.0	30	31.9	46	48.9
Women	160	82	51.3	13	8.1	95	59.4	45	28.1	20	12.5	65	40.6
Hispanics													
Men	47	22	46.8	3	6.4	25	53.2	9	19.1	13	27.7	22	46.8
Women	82	41	50.0	7	8.5	48	58.5	24	29.3	10	12.2	34	41.5
Marital status[d]	503												
Never married	284	127	44.7	16	5.6	143	50.4	60	21.1	81	28.5	141	49.6
Married	93	35	37.6	9	9.7	44	47.3	34	36.6	15	16.1	49	52.7
Separated, divorced, annulment	109	60	55.0	8	7.3	68	62.4	24	22.0	17	15.6	41	37.6
Widowed	17	10	58.8	1	5.9	11	64.7	5	29.4	1	5.9	6	35.3
DSM-III diagnosis[e]	382												
Schizophrenia	68	42	61.8	2	2.9	44	64.7	7	10.3	17	25.0	24	35.3
Affective disorders	47	27	57.4	4	8.5	31	66.0	6	12.8	10	21.3	16	34.0
Adjustment disorders	71	43	60.6	2	2.8	45	63.4	15	21.1	11	15.5	26	36.6
V codes	89	10	11.2	2	2.2	12	13.5	58	65.2	19	21.3	77	86.5
Other axis I disorders	71	38	53.5	10	14.0	48	67.6	6	8.5	17	23.9	23	32.4
Axis II disorders	36	19	52.8	2	5.6	21	58.3	5	13.9	10	27.8	15	41.7
Source of referral[f]	503												
Self	105	57	54.3	9	8.6	66	62.9	26	24.8	13	12.4	39	37.1
Family	101	39	38.6	3	2.9	42	41.6	45	44.6	14	13.9	59	58.4
Mental health system	152	71	46.7	4	2.6	75	49.3	26	17.1	51	33.6	77	50.7
Court	30	3	10.0	0	0.0	3	10.0	7	23.3	20	66.7	27	90.0
Other health agency	98	56	57.1	17	17.3	73	74.5	17	17.3	8	8.2	25	25.5
Other	17	6	35.3	1	5.9	7	41.2	2	11.8	8	47.0	10	58.8
Use of psychiatric services	382												
No previous use[g]	138	50	36.2	12	8.7	62	44.9	54	39.1	22	15.9	76	55.1
More than 10 visits[h]	185	108	58.4	7	3.8	115	62.2	35	18.9	35	18.9	70	37.8

[a]There was a significant difference in the mean±SD ages of the subjects with complaints related to mental state (35.2±13.7 years), physical functioning (35.7±10.4 years), social relations (32.8±14.6 years), and social performance (31.0±11.8 years) ($F=4.2$, $df=1, 3$, $p<0.01$).
[b]Initial complaints were made by 503 subjects, but only 382 kept their appointments.
[c]$\chi^2=46.9$, $df=15$, $p<0.001$.
[d]$\chi^2=23.6$, $df=9$, $p<0.01$.
[e]$\chi^2=122.6$, $df=15$, $p<0.001$.
[f]$\chi^2=17.7$, $df=15$, $p<0.001$.
[g]$\chi^2=28.0$, $df=3$, $p<0.001$.
[h]$\chi^2=20.0$, $df=3$, $p<0.001$.

subsequent use of outpatient psychiatric services was measured as the number of subsequent outpatient visits after the initial contact with the clinic. The number of visits ranged from 1 to 175, and the median was 10.

The proportion of variance in log number of visits accounted for by all the variables included in the analysis (R^2) was 0.25. The four best predictors were diagnostic group ($R^2=0.1485$, $F=13.1$, $df=5$), source of referral ($R^2=0.0765$, $F=7.6$, $df=5$), previous use of psychiatric services ($R^2=0.0835$, $F=34.6$, $df=1$), and type of presenting complaint ($R^2=0.0571$, $F=7.6$, $df=3$). The application of the maximum R^2 improvement model, both including and excluding the 27 patients whose outpatient admissions eventually led to inpatient transfer, revealed that the increment in the proportion of variance accounted for produced by type of presenting complaint was relatively small. When the subjects transferred to inpatient psychiatry were included, R^2 improved from 0.2016 to 0.2121; when they were excluded, R^2 improved from 0.2188 to 0.2305.

DISCUSSION

In this study the characteristics that distinguished subjects who came with medical complaints from those who came with social complaints were female gender, nonwhite race/ethnicity, self-referral, older age, and being widowed, separated, or divorced or having an annulled marriage. These findings suggest that sociocultural factors and/or interpersonal difficulties are important in the production of presenting complaints.

The type of presenting complaint was meaningfully related to the type of referral source. Also, the type of complaint was significantly related to the previous use of psychiatric services only when the complaints were classified into the four categories used in this research. These relationships illustrate the importance of classifying complaints as shown here instead of simply grouping them into "medical" and "social." Indeed, the presenting complaints may be a function of familiarity with the mental health system or learning to say "the right thing" to gain admission.

The proportions of subjects presenting with medical or social complaints were approximately the same among all diagnostic groups. This distribution seems to indicate that complaint type is not solely a function of the specific psychopathological state present at the time of the request for admission to the clinic. Important intervening variables, such as the severity of mental disorders and the availability and adequacy of social supports, were not measured and may account for this finding to some extent. There is some indication, however, that the patient's specific complaint may be reflected in conditions not attributable to a mental disorder, assigned *DSM-III* V codes. These subjects understandably presented more social complaints than medical, but even within this group, 13% presented with medical complaints, apparently insufficient to warrant *DSM-III* diagnoses. With the possible exception of *DSM-III* V codes, diagnosis or psychopathological state is not a major determinant of the type of presenting complaint.

Individuals presenting with social complaints tended to be low users of services, while those presenting with medical complaints were likely to be high users. Interpersonal crises are more likely to be treated with short-term, focused therapies and are more easily resolved than other problems; therefore, they may require fewer visits. Alternatively, the low users may have terminated their treatment earlier because their needs were unmet.

The variables included in the analysis accounted for 25% of the variance in the number of outpatient visits. This leaves 75% of the variance unexplained. Factors unexplored in this study, such as the reasons for termination of treatment, the type of therapy received, and the severity of the mental disorder are potentially explanatory variables. In addition, clinicians' opinions about the patients' presenting complaints and patients' areas of functioning may contribute to the volume of outpatient services. Future research might investigate these variables and their relationship to use of psychiatric outpatient services.

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DSM-III Personality Disorders and the Outcome of Treated Panic Disorder

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Fifty-two patients with panic disorder who had been receiving active benzodiazepine treatment for 8 weeks were assessed by using the outcome measures of spontaneous and situational panic attacks, scores on the Hamilton scales for anxiety and for depression, and scores on self-rated disability scales. Although spontaneous panic attacks were not affected by the presence of any personality disorder, the remaining outcome measures showed a strong and negative association with DSM-III *antisocial, borderline, histrionic, and narcissistic personality disorders. There was also a mild negative association with avoidant personality disorder. A subgroup of patients with both major depression and panic disorder appeared more strongly affected.*

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Although there has been some empirical research on the effect of personality on treatment outcome in depression, to our knowledge there have been no reports on the effect of *DSM-III* personality disorders on the outcome of panic disorder. Kerr et al. (1) found a relationship between the outcome of endogenous and reactive depression and Maudsley Personality Inventory scores. They found Maudsley Personality Inventory neuroticism scores to be higher in the poor outcome group both initially and at 4-year follow-up. Weissman et al. (2), in a prospective study of 150 treated depressed female outpatients, found that Maudsley Personality Inventory neuroticism scores predicted clinical outcome and that scores in the good outcome group were still significantly lower than those in the poor outcome group when measured at 8- and 20-month follow-up. This was in spite of the general overall improvement in clinical status of the entire group. In a treatment study of a mixed group of patients who had been treated with phenelzine, Tyrer et al. (3, 4) used the Personality Assessment Schedule (3) to determine the presence or absence of a personality disorder. They found personality disorder to be a significant negative predictor of outcome (4). Faravelli et al. (5), in a study of relapse from treated major depressive episodes, found that scores on the Maudsley Personality Inventory neuroticism scale predicted patient relapse, and Zimmerman et al. (6) found that a *DSM-III*-defined personality disorder predicted poorer outcome at 6-month follow-up for psychiatric inpatients with major depression who had received ECT.

The purpose of this report was to determine whether the presence of a *DSM-III* personality disorder measured by standardized techniques would influence the outcome of pharmacologically treated panic disorder. I hypothesized a poor outcome for patients who had a personality disorder.

METHOD

Subjects and Measures

The subjects used in this investigation were volunteers with *DSM-III*-defined panic disorder who were recruited by advertising to participate in a drug treatment study of panic disorder. Patients who were enrolled had to pass both a telephone screen and an interview by a psychiatrist using the Structured Clinical Interview for *DSM-III* disorders (SCID) (7). Patients were required to have panic disorder and were excluded if they had organic brain syndrome, mental retardation, school phobia, major depression that predated or dominated the panic disorder picture, or drug or alcohol abuse in the last year. There were 52 patients in active treatment in the study (28 treated with alprazolam and 24 treated with diazepam). In addition, a placebo group of 28 subjects was used to determine whether treatment was superior to placebo overall. All subjects provided informed consent to participation in the study after its nature had been explained.

At baseline and week 8 of treatment, the Hamilton Rating Scale for Anxiety and the Hamilton Rating Scale for Depression were administered, the number of spontaneous panic attacks in the last week were counted, and measures of work and social disability (10-point Likert scales) were administered. All of these

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measures have been used successfully in previous treatment studies.

Three measures of personality disorders were used, two self-report and one interview. The first self-report measure was the Personality Diagnostic Questionnaire (8). This is a 152-item self-administered, forced-choice, true-false diagnostic instrument measuring all 11 *DSM-III* personality disorders. The test-retest of psychiatric outpatients at 1 month yielded kappas of 0.56 or above for paranoid, schizotypal, antisocial, borderline, avoidant, and compulsive disorders (9).

The second self-report was the Millon Clinical Multiaxial Inventory (10), a 175-item forced-choice, true-false self-report instrument. The reliabilities of this measure's personality scale at 4 to 6 weeks ranged from 0.77 to 0.85 in psychiatric patients (10). The personality scales of the Millon inventory appear to be strongly related to but not identical with the *DSM-III* axis II disorders (11).

The interview instrument used was the Structured Interview for *DSM-III* Personality Disorders (12), a 160-item semistructured interview measuring *DSM-III* axis II disorders. When the patient's axis I disorder is known, this interview takes 60 to 90 minutes to administer. As recommended by the instrument's developer, an informant was also interviewed. The joint interview kappa for presence or absence of a personality disorder was 0.71. Individual personality disorder joint kappas were 0.85 for borderline, 0.75 for histrionic, 0.62 for schizotypal, 0.45 for avoidant, and 0.90 for dependent (13).

Procedure and Analyses

After being enrolled in the study all patients were maintained off all antianxiety medication for 1 week. At the end of this week baseline measures were taken and personality measures were administered. Patients were then blindly assigned to a medication (diazepam 10 mg, alprazolam 1 mg, or placebo). Patients received from one to 10 pills of study medication a day. The dose was adjusted upward until either all panic disorder symptoms disappeared or side effects precluded further raises in dose. Patients were seen at the end of weeks 1, 2, 3, 4, 6, and 8.

The six measures of improvement used were the proportional changes in the following scores: Hamilton anxiety scores and Hamilton depression scores, the number of spontaneous panic attacks in the last week, the number of situational panic attacks in the last week, work disability scores, and social leisure disability scores. These proportional change scores were calculated by taking the baseline score, subtracting the score obtained during the last treatment week, and dividing the result by the baseline score.

Personality measures that were dichotomous were compared with outcome measures by using t tests. Continuous personality measures were correlated with the outcome measure by using Pearson's correlation technique.

Structured Interview for *DSM-III* Personality Disorders variables and Personality Diagnostic Questionnaire variables were also analyzed by presence or absence of any personality disorder. Since there is now some evidence for the validity of the *DSM-III* personality clusters (14–16), Structured Interview for *DSM-III* Personality Disorders and Personality Diagnostic Questionnaire personality disorder variables were also arranged into clusters. If any personality disorders were present within the cluster, the patient was considered to have that cluster. The schizoid cluster (cluster A) includes the schizoid, schizotypal, and paranoid disorders, the dramatic cluster (cluster B) includes borderline, narcissistic, histrionic, and antisocial disorder, and the anxious cluster (cluster C) includes avoidant, dependent, passive/aggressive, and compulsive disorders.

Since I was interested only in the effect of personality on treated panic disorders, I compared the treated groups and the placebo group to ascertain major differences in outcome. Any detailed analysis of alprazolam compared with diazepam and placebo will be performed later by a different group of authors and is beyond the scope of this paper.

To avoid unnecessary redundant tests the sample sizes of the patients with and without personality disorders were examined before analysis and only those with a large enough sample size were analyzed. As a further safeguard, only results significant at the 0.01 level will be considered significant here, although lesser values may be reported for clinical interest.

Finally, it appeared possible that within the treated group the patients with major depression or those who had dropped out after having completed only 3 weeks of treatment might represent a separate confounding group. Personality outcome analyses were run again without this group, and it was compared with the rest of the group on baseline variables.

RESULTS

The alprazolam and diazepam groups did not differ in baseline or outcome variables, so I combined them into one group—the treatment group—and I will report their results together. There were 52 patients in this group. Their mean±SD age was 39.0±9.9 years, and their mean age at onset of the disorder was 26.5±9.8 years. Twenty-seven (52%) were women, 19 (37%) had extensive phobic avoidance (agoraphobia), and 21 (40%) had limited phobic avoidance. Nineteen (37%) of the 52 patients had any Personality Diagnostic Questionnaire disorder: 12 (23%) of the 52 had the schizoid cluster, 14 (27%) had the dramatic cluster, 17 (33%) had the anxious cluster, 10 (19%) had avoidant disorder, and 13 (25%) had dependent disorder. Twenty-one patients (40%) had any Structured Interview for *DSM-III* Personality Disorders disorder: four (8%) had the schizoid cluster, eight (15%) had the dramatic cluster, and 18 (35%) had the anxious clus-

ter. The sex distribution of the patients with personality disorders roughly paralleled that of those without any personality disorder.

The 28 patients in the placebo group did not differ significantly from the treatment group on age, sex ratio, age at onset of the disorder, percent with agoraphobia, and baseline symptom measures. They did differ on the following outcome measures: change in spontaneous panic attacks, 0.52 versus 0.77 ($F=7.44$, $df=1, 44$, $p<0.01$); situational anxiety attacks, 0.48 versus 0.78 ($F=7.50$, $df=1, 45$, $p<0.01$); and work disability, 0.46 versus 0.76 ($F=7.15$, $df=1, 46$, $p<0.01$).

Seven patients in the treatment group had major depression; three of these dropped out after completing only the first 3 weeks of the study. Although this group did not differ from the rest of the treatment group in mean age at onset of panic disorder or sex ratio (five women and three men), they did differ on some variables. They had a significantly higher initial Hamilton anxiety score (27.8 ± 6.9 versus 18.0 ± 8.4; $F=7.20$, $df=1, 46$, $p<0.01$). They also showed trends toward greater initial depression on the Hamilton depression scale (scores of 27.8 ± 6.9 versus 16.5 ± 5.7; $F=4.9$, $df=1, 46$, $p<0.03$) and greater social disability (scores of 9.5 ± 0.6 versus 4.9 ± 2.7; $F=5.3$, $df=1, 46$, $p<0.025$). On the outcome variables there was a strong trend for them to do more poorly in number of situational panic attacks (0.90 ± 0.3 versus 0.19 ± 0.8; $F=5.01$, $df=1, 30$, $p<0.04$). On Structured Interview for *DSM-III* Personality Disorders measures this group had more disorders overall (86% versus 37%; $p=0.03$, Fisher's exact test) and more anxious cluster disorders (86% versus 29%; $p<0.01$, Fisher's exact test). In general this group appeared to be sicker, to have more personality disorders, and to be less responsive to treatment.

Presence of the Structured Interview for *DSM-III* Personality Disorders dramatic cluster significantly distinguished groups by number of situational panic attacks (0.62 versus 0.81, $t=3.4$, $df=34$, $p=0.001$). Presence of the Personality Diagnostic Questionnaire dramatic cluster also differentiated groups by Hamilton anxiety scores (0.46 versus 0.69, $t=2.5$, $df=48$, $p<0.01$), and work disability scores (0.27 versus 0.81, $t=2.44$, $df=41$, $p<0.0001$). The Personality Diagnostic Questionnaire diagnosis of avoidant personality disorder significantly differentiated groups by Hamilton anxiety scores (0.51 versus 0.75, $t=2.92$, $df=47$, $p<0.005$), Hamilton depression scores (0.44 versus 0.68, $t=2.15$, $df=49$, $p<0.025$), and social leisure disability scores (0.41 versus 0.78, $t=2.85$, $df=50$, $p<0.005$). The Personality Diagnostic Questionnaire diagnosis of histrionic personality disorder also showed significant differences for number of situational panic attacks (0.64 versus 0.80, $t=3.75$, $df=33$, $p<0.0005$), work disability scores (0.27 versus 0.78, $t=2.15$, $df=38$, $p<0.025$), and social disability scores (0.36 versus 0.77, $t=3.82$, $df=47$, $p<0.0005$).

Correlations for the scaled scores on the Millon inventory showed trends between histrionic disorder and situational panic attacks ($r=-0.28$, $p<0.04$), Hamilton anxiety scores ($r=0.30$, $p<0.03$), and work disability scores ($r=-0.24$, $p<0.05$).

When the personality outcome analysis was run without the depressed-dropout groups, the results were in the same direction, only less powerful. The Personality Diagnostic Questionnaire dramatic cluster no longer significantly distinguished Hamilton anxiety and work disability scores. (Significantly distinguishing means a p value of less than 0.01; although p values of more than 0.01 are reported in this section, this is done only for clinical interest.)

DISCUSSION

The findings from the previous studies of personality and the outcome of major depression would suggest similar findings for panic disorder, and this has turned out to be the case. All three personality instruments indicated poor response to treatment for patients having *DSM-III* flamboyant (dramatic) personality disorders. This can be taken as a strong positive finding. The fact that two instruments found an association with an individual anxious cluster personality disorder indicates the need for further investigation in that cluster. Perhaps the most interesting thing about these findings is their specificity. The Structured Interview for *DSM-III* Personality Disorders and the Personality Diagnostic Questionnaire did not show a significant association for presence or absence of any personality disorder, nor did any of the three instruments indicate associations with the *DSM-III* schizoid personality disorder cluster. It may well be that although some personality disorders affect the outcome of treated panic disorder strongly, others may have no influence at all. Almost as interesting as the fact that personality disorders influenced outcome is the question of which outcomes were influenced. No personality measures influenced spontaneous panic attacks, although several did influence situational panic attacks, Hamilton anxiety and depression scores, and the disability scores. It may be that only variables which have a distinct environmental component (i.e., situational but not spontaneous panic attacks) will be influenced by personality variables.

The finding that there was a subgroup of patients with dual diagnoses (major depression and panic disorder) that was sicker, tended to drop out of treatment, tended to have more personality disorders, and tended to have a poorer response to treatment is not surprising in retrospect. Patients with two diagnoses would be expected to be sicker, and patients with one or more disorders to have a greater chance of having other psychiatric disorders, including personality disorders. What is important is that there might be a disproportionate effect on outcome of personality analyses in these patients. It is important to know that these patients tend to select themselves out of treatment. A research study that is too demanding in terms

of the time a patient needs to remain in the study to be counted might miss the personality effect entirely. Clinically these patients would need extra support to successfully complete standard treatment.

A possible confounder of my findings is the lack of a control group that has been given a tricyclic antidepressant. There is some clinical evidence that patients with disorders in the dramatic personality disorder cluster become inappropriately disinhibited when given benzodiazepines. This is a possible alternate explanation for some of the study's results.

Strengths of this study include its double-blind design (neither investigators nor subjects knew whether they were receiving placebo, diazepam, or alprazolam) and its structured measurement of *DSM-III* personality disorders. Weaknesses include the relatively short period of time patients were in treatment, the relatively small sample size, and the failure to have a tricyclic antidepressant comparison group. (These limitations make this study preliminary.) These areas could be fruitfully investigated in further studies.

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DST Results in Nonpsychotic Depressed Outpatients

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In two studies using the dexamethasone suppression test (DST) to evaluate the efficacy of newer antidepressants in depressed outpatients, the authors found a DST nonsuppression rate of 13% (11 of 86 patients). Thirty-three of the DST suppressors received an antidepressant and 42 received placebo; the drug-treated group showed a significant therapeutic response. The low rate of DST nonsuppression in these depressed outpatients, a finding consistent with that of other investigators, does not confirm or refute reports that these patients are relatively resistant to placebo in comparison with active medication. The authors recommend that DST results not be used as selection criteria in studies assessing newer therapies for depressed outpatients.

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During the past decade, there has been controversy over the clinical utility of measuring cortisol nonsuppression in depressed patients following administration of a 1- or 2-mg dexamethasone suppression test (DST). Most studies of this phenomenon have focused on subjects who are severely depressed inpatients (1–3).

Several studies comparing DST status and treatment response (1, 4) have suggested that nonsuppressors respond better to antidepressant therapy than do suppressors. In a review of the literature, Arana et al. (1) reported a favorable response to antidepressant drugs in 76% to 82% of nonsuppressors compared with 64% to 74% of suppressors. Several independent studies (5–7) have suggested that DST nonsuppression is also singularly predictive of poor placebo response; two of these studies (6, 7) reported results from hospitalized subjects. Furthermore, the work of Shrivastava et al. (8) implies that DST suppressors are excessively prone to placebo response. If DST nonsuppression is indeed predictive of poor placebo and psychotherapy response (9) and a relatively greater drug response, then this marker could be used to advantage in selecting patients for clinical trials of new antidepressant medications, even though the test does not appear to aid in the diagnosis and treatment of individuals. Such clinical applicability is possible only if the results of previous studies (7, 8) hold true for the outpatient population, which accounts for the vast majority of patients treated for depression. In an unpublished survey conducted by R. Rudolph, M.D., in 1987, only 18% (N=2,707) of 14,962 prescriptions for tricyclic antidepressants were for hospitalized patients. Furthermore, only about 29% (N=4,254) of 14,720 new prescriptions for antidepressants in the survey were written by psychiatrists.

In this report we will attempt to establish the frequency of abnormal DST results in depressed outpatients and to clarify whether DST suppressors are likely to show a higher rate of placebo response and a lower rate of antidepressant response than nonsuppressors.

METHOD

The subjects were 139 moderately to severely depressed outpatients enrolled in one of two multicenter, placebo-controlled studies of new antidepressants at the Harborview Medical Center in Seattle, Wash., between 1982 and 1984. All subjects consented to participation in the studies after the procedures had been explained to them. Both studies were double-blind and were preceded by a period of 2 to 10 days (average of 7 days) of placebo washout. During this time the patients were free of psychoactive drugs. At the end of this period, patients were randomly assigned to either drug or placebo treatment for a 6-week clinical trial. One study compared the clinical outcomes of patients given either placebo or adinazolam (up to 60 mg/day). The other compared results of placebo administration versus imipramine (150–225 mg/day) or fluvoxamine treatment. For this report we combined the placebo groups from the two studies for our placebo group

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(N=48) and compared them with the groups of patients given adinazolam and imipramine (N=38). The results of the study of placebo and adinazolam alone have been reported elsewhere (10).

Inclusion criteria consisted of age between 18 and 70 years, a diagnosis of unipolar major depression by *DSM-III* criteria, and a Hamilton Rating Scale for Depression (11) score of at least 21 at screening that did not drop by more than 20% by the end of the placebo washout period. Patients were excluded if they met criteria for psychosis or other *DSM-III* axis I diagnoses besides major depression, including alcohol or drug abuse. In addition, they were evaluated with a complete physical examination and laboratory studies consisting of CBC, urinalysis, SMA-12, ECG, and thyroid function tests. Subjects were excluded for substantial medical illness, endocrinopathy, pregnancy, or taking medications known to affect DST results, such as anticonvulsants or benzodiazepines. Each patient was screened by a faculty psychiatrist at Harborview Medical Center. The interview included a uniform review of psychiatric history by relevant probe questions for major syndromes, including schizophrenia, organic brain syndromes, mania, substance abuse disorders, generalized anxiety disorder, panic disorder, phobic disorders, posttraumatic stress disorder, obsessive-compulsive disorder, anorexia nervosa, bulimia, and antisocial personality disorder. Every attempt was made to have the same physician conduct the weekly follow-up rating session.

Eighty-six patients were given a DST at the end of the placebo washout period. Patients were given 1 mg of dexamethasone and instructed to take it at 11:00 p.m. Between 2:00 and 4:00 p.m. the following day, blood samples were drawn to determine serum cortisol levels. Serum cortisol levels were measured by using a clinical assays radioimmunoassay kit. The characteristics of this assay have been reported for a separate, previously studied sample of depressed outpatients from our institution (12). Cortisol values greater than or equal to 4.0 μg/dl were considered nonsuppression, based on results of a previous sample from our laboratory and reports of others (5, 13).

Treatment outcome was measured in three ways: Hamilton depression scale scores at the end of the 6-week study period or the last visit, percentage of patients with a 50% or greater drop in Hamilton depression scale scores at the end of the study who had a final score of 10 or less, and pattern analysis of the clinical global impression (CGI) scale with an emphasis on persistent response as described by Quitkin et al. (14). All t tests were two-tailed and validated for homogeneity of variance by using an F test.

RESULTS

DST results were available for the 48 subjects receiving placebo, six (13%) of whom were nonsuppressors, and the 38 subjects receiving antidepressants, five (13%) of whom were nonsuppressors. Among the patients receiving an antidepressant, 32 were given adinazolam and six were given imipramine. The overall nonsuppression rate was 13% (11 of 86 patients). A more conventional nonsuppression value of more than 5.0 μg/dl would have yielded an overall nonsuppression rate of 6% (five of 86 patients).

TABLE 1. Characteristics of Depressed Outpatients Who Did or Did Not Suppress Cortisol on the DST

Characteristic	Suppressors (N=75)	Nonsuppressors (N=11)
Age at presentation (years)[a]		
Mean	43.1	34.9
SD	11.7	7.9
Age at onset of illness (years)[b]		
Mean	31.7	23.6
SD	13.4	12.2
Female		
N	41	4
%	54.7	36.4
Past history of depression		
N	45	8
%	60.0	72.7
Duration of illness (months)		
Mean	35.3	26.6
SD	60.3	22.5
Severity of endogenous symptoms (combined score on guilt, psychomotor disturbances, and weight loss items of Hamilton depression scale)		
Mean	5.5	5.4
SD	1.5	1.1
Substantial psychomotor retardation		
N	25	3
%	33.3	27.3
Anergia (score on fatigue item of Hamilton depression scale)		
Mean	2.0	2.0
SD	0.2	0.0
Weight loss		
N	14	1
%	18.7	9.1
Initial Hamilton depression scale score[c]		
Mean	24.6	26.8
SD	3.5	3.3
Initial clinical global impression score[d]		
Mean	4.3	4.6
SD	0.5	0.5

[a] $t=2.24$, df=84, $p=0.02$.
[b] $t=1.88$, df=83, $p=0.06$.
[c] $t=1.94$, df=84, $p=0.06$.
[d] $t=1.97$, df=84, $p=0.05$.

As shown in table 1, suppressors and nonsuppressors did not differ significantly with respect to sex, past history of depression, duration of illness, severity of endogenous symptoms, substantial motor retardation, anergia, or weight loss. Nonsuppressors showed a trend toward greater severity of illness as judged by the initial Hamilton depression scale scores and the initial CGI scores. Nonsuppressors in our sample were significantly younger than suppressors at presentation. It

TABLE 2. Outcome of Depressed Outpatients Who Did or Did Not Suppress Cortisol on the DST Who Were Then Given Placebo or an Antidepressant[a]

Variable	Suppressors (N=75)		Nonsuppressors (N=11)	
	Placebo (N=42)	Antidepressant (N=33)	Placebo (N=6)	Antidepressant (N=5)
Initial Hamilton depression scale score				
Mean	24.8	24.4	24.4	26.6
SD	3.7	3.4	3.4	4.0
Initial clinical global impression scale score				
Mean	4.3	4.4	4.5	4.8
SD	0.5	0.5	0.5	0.4
Quit before end of study				
N	23	12	3	2
%	54.8	36.4	50.0	40.0
Hamilton depression scale score at end of study				
Mean	15.9[b]	10.6[b]	17.5	13.8
SD	8.9	8.6	7.8	13.6
Hamilton depression scale score dropped 50% or more by end of study				
N	15[c]	21[c]	2	3
%	35.7	63.6	33.3	60.0
Improved according to criteria of Quitkin et al. (14)				
N	9[d]	16[d]	1	3
%	21.4	48.5	16.7	60.0

[a]Thirty-two patients were given adinazolam; six were given imipramine.
[b]$t=2.8$, df=73, $p<0.01$.
[c]$\chi^2=6.4$, df=1, $p<0.05$.
[d]$\chi^2=10.1$, df=1, $p<0.01$.

is known that the DST nonsuppression rate is higher among both depressed and normal control subjects older than 60 years of age (1). Our study contained only six subjects older than 60, all of whom were suppressors. Another explanation would be that a number of our patients were actually suffering from bipolar affective disorder. However, none of the patients had a history of mania, and the suppressors and nonsuppressors did not differ with respect to symptoms associated with bipolar disorder, such as acute onset, psychomotor retardation, or anergia (see table 1). Hypersomnia was not directly assessed.

Table 2 shows the results of administration of placebo or an antidepressant in DST suppressors and nonsuppressors. Outcome measures, including the percentage of subjects showing a 50% or greater drop in Hamilton depression scale scores who had a Hamilton depression scale score of 10 or less at the end of the study, mean total Hamilton depression scale scores at the end of the study, and pattern analysis of response according to the criteria of Quitkin et al. (14), were not significantly different between suppressors and nonsuppressors treated with either placebo or an antidepressant. We were unable to demonstrate a superior response to antidepressants over placebo in the DST nonsuppressor group by using the same measures. However, the sample size of nonsuppressors was not great enough that nonsignificant differences in any comparison involving them would have any meaning.

Using the criteria already described, we found that the DST suppressors showed a significantly better therapeutic response to antidepressants than to placebo (see table 2). Sixty-four percent of the suppressors receiving antidepressants showed a 50% or greater drop in Hamilton depression scale scores and had a final score of 10 or less, compared with only 36% of the patients in the placebo-treated group (table 2). To determine whether these results reflected a preferential response among DST suppressors to an anxiolytic agent such as adinazolam, the imipramine and adinazolam groups were analyzed separately. In fact, the 27 suppressors treated with adinazolam showed a less favorable response to treatment than the six treated with imipramine: 16 (59%) of the suppressors given adinazolam compared with four (67%) of the suppressors given imipramine had a 50% drop in Hamilton depression scale score and a score of 10 or less at the end of study, and 10 (37%) versus three (50%) met persistent response criteria (14). The placebo response rate of the suppressor group ranged from 21% to 36% depending on the criteria used.

DISCUSSION

In this group of 86 nonpsychotic depressed outpatients, the DST nonsuppression rate was very low (13%) when we used a serum cortisol level of 4.0 μg/dl as the criterion for nonsuppression. This is consistent with other literature regarding outpatient studies: DST nonsuppression rates are often lower than those for similar inpatient studies. Review of seven outpatient studies (5, 12, 13, 15–18) showed a nonsuppression rate ranging from 13% to 49% with an average of 21% (109 of 508 patients). In contrast, seven inpatient studies (4, 6, 7, 15, 19–21) reported nonsuppression rates between 30% and 72% with an average of 54% (392 of 724 patients). This discrepancy is undoubtedly multifactorial and cannot be fully explained at the present time. Differences in the severity of illness and the methods of obtaining DST results in the two groups are probable contributors.

The results of our study indicate that DST suppressors, who constitute the majority of depressed outpatients, show a significant and clinically meaningful response to antidepressants compared with placebo. Although a similar trend was seen in DST nonsuppressor subjects, the number of such patients was so small as to make the comparison very risky. We were unable

to replicate the findings of Shrivastava et al. (8) showing an unexpectedly high placebo response rate among DST suppressors.

Arana et al. (1), in their review of 18 studies performed before 1985, reported differences in acute somatic therapy response among DST nonsuppressors (76% to 82%) and suppressors (64% to 74%). This difference, although significant on first analysis, did not reach statistical significance (22) by the stricter Mantel-Haenszel method of analysis. We think that this difference is of limited clinical utility. The role of cognitive therapy alone in DST suppressors is not well established: there is only one study (9) reporting results of treatment in nine patients. It is our impression that antidepressants are clinically useful therapeutic tools in depressed patients with DST suppression and that exclusion of these patients from clinical trials assessing antidepressant activity or the comparison of somatic therapies versus psychotherapies would severely limit the interpretation of these studies due to lack of generalizability.

CONCLUSIONS

In summary, the DST nonsuppression rate was very low in our sample, a finding generally seen in depressed outpatients. Therefore, we were unable to demonstrate a singularly poor placebo response rate and high antidepressant response rate in the DST nonsuppressor group. DST suppressors showed a persistent and clinically significant response to antidepressants compared with placebo and failed to show an abnormally high placebo response rate. It is our conclusion that DST suppressor and nonsuppressor subjects alike should be included in clinical trials evaluating pharmacotherapies and psychotherapies for depressed outpatients.

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Book Forum

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PSYCHODYNAMICS AND PSYCHOANALYSIS

Progress in Self Psychology, vol. 2, *edited by Arnold I. Goldberg. New York, Guilford Press, 1986, 313 pp., $30.00.*

Heinz Kohut, a researcher in psychoanalysis, created a stir when he presented "The Two Analyses of Mr. Z" in 1979 (1). Kohut described how, after a traditional analysis with "good results," Mr. Z returned 4½ years later for a second analysis, which spawned self psychology. A bitter debate followed publication of this article on whether self psychology is psychoanalysis. Dr. Goldberg, in his preface, states that Kohut asked colleagues to answer critics of his work. Volume 2 is the second collection of the resulting essays. It is divided into four sections: Theoretical Issues, Clinical Problems, Development, and Original Papers. The essays are by a most impressive list of researchers in both psychoanalysis and self psychology. A general summary and specific references to authors and their contributions follow.

Self psychology emphasizes that pathogenesis is based on empathic deprivation—parental failure. The self develops separately from drives and is a supraordinate bipolar central mental structure composed of grandiose self (ambition) and the internalized idealized parent (ideals). "Tragic Man" needs "selfobjects" all of his life "just as he needs oxygen."

Although originally intended for narcissistic and self-disorders, self psychology is now believed to be widely applicable. In therapy patients experience "transmuting internalization" through transferences facilitating the resumption of development. Added to the traditional psychoanalytic tools of interpretation and working through, empathy leads to the gratification of being understood, thereby enhancing in-depth exploration. Psychoanalysis is considered rigid, its practitioners are seen as objectionably neutral, abstinent, and steeped in morality, and its patients are viewed as "hectored." Self psychology rejects intrapsychic centrality and the avoidance of nonanalytic maneuvers.

Psychoanalytic purists criticize self psychology as an appealing but misleading model that is ambiguous, vague, mystical, abstract, and sanitized of lust and rage. It minimizes or rejects the centrality of instincts, conflicts, the Oedipus complex, defense, and resistance. It is clarifying, not interpretative. Empathy is ego supportive, transference gratifying, nurturing, and reeducational. It is psychotherapy and not psychoanalysis.

H.D. Curtis, on examining an illustrative case, finds that sexual conflict is "resolved" without insight through the patient's renouncing men and becoming a physician. He contends that self psychology is a disservice to the neurotic patient in need of psychoanalysis. M.F. Basch claims that psychoanalysis has changed from an intrapsychic to an interpersonal perspective. Markson and Thompson, classically trained analysts, support the use of empathy but view sexuality and aggression as drives and not disintegration products. Stolorow accuses psychoanalysis of uncritical adherence to the mechanistic doctrine of instinctual drives. In a later paper, he clarifies the meaning of self and "selfobject" as structures of psychological functions. In rejoinder, Curtis denies that psychoanalysis has strayed toward the interpersonal.

Wallerstein regards self psychology as psychoanalytically oriented but not mainstream psychoanalysis, an exercise in emphasis rather than substance. Wolf contends that self psychology is misread and that analysts fear becoming involved with patients through empathy. P.H. Tolpin believes that the disagreement between Wallerstein and Kohut is the latter's repositioning of the drive conflict model within the supraordinate framework of the self. M. Tolpin points to the infant's self-righting capacities and the search for the self or "selfobject" tie through empathy. Ornstein discusses separation anxiety and the calming effect of transitional objects through transmuting internalization. Lichtenberg refers to the perceptual-affective-action pattern with the liberation of compulsive repetition of hope through empathy. Both M. and E. Shane apply self psychology in adolescence and insist that traditional psychoanalysis is limited and that Kohut corrected the notion of phallocentrism. Kay defends the insights of self psychology.

Sloane recommends the use of empathy to avoid narcissistic injury in the supervision of residents; this contrasts with Wallerstein's focus on confrontation and correction. Rickles finds that psychoanalysis is not beneficial for psychosomatic disorders. Symbolism is absent in self disorders and interpretation results in narcissistic injury. Reiser declares that in suicidal problems, the self needs a nourishing milieu to overcome feelings of emptiness. Brandshaft protests that U.S. analysts ignore British contributions on object relations. Dissatisfaction with therapeutic results of traditional psychoanalysis has led to eclecticism. Innovations by M. Klein have been extended by Balint, Fairbairn, and Winnicott. Muslin states that self psychology relies on the same tools as traditional psychoanalysis, but the curative goal is to seek out and to be sustained by appropriate "selfobjects" through empathic resonance with them. Detrick differentiates twinship and alter ego transference; the former leads to sameness and the acquisition of skills and the latter fixates in the group.

Dissatisfied with the therapeutic results of psychoanalysis, Kohut introduced empathy and dismissed some basic psychoanalytic concepts. Freud (2) also recommended a change—"the copper of suggestion"—to reach more of the sick. Pure analysis is illusory, as shown by the Menninger Project (3), but, to the purist, self psychology is not psychoanalysis. I believe this is so on the basis of my experience. But does it really matter? Why quarrel with the success of self psychology compared with other therapies as shown with follow-up studies, which should be emphasized in updating material?

This is a book of substance. Goldberg has fulfilled Kohut's aim and leaves the reader well informed to decide about the value of self psychology. It is stimulating and provides an opportunity to view searching minds in debate. The book has a substantial bibliography, a workable index, and illustrative

cases and is recommended for psychiatric residents, faculty, practitioners, psychologists, and the interested public.

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States of Mind: Configurational Analysis of Individual Psychology, 2nd ed., *by Mardi J. Horowitz. New York, Plenum, 1987, 270 pp., $39.50.*

This volume updates the method Horowitz applies to the study and evaluation of psychotherapy, which he calls "configurational analysis." In the first edition of this book (1979), Horowitz's aim was to synthesize diverse modes of psychodynamic, object relations, and cognitive perspectives. Thus, he chose the term "configurational analysis," which had been used by Erik Erikson (1) to cover the many psychoanalytic frames of reference one must coordinate in order to understand the formation of a dream. Horowitz now reports that experience with his method by trained colleagues as well as himself has sustained its major features and created enough new material to warrant a second edition. The most revision has occurred in the study of the formulation of maladaptive and recurrent interpersonal relationship patterns based on inferences about self-concepts and role relationship models. The additional theoretical material came from discussion between psychodynamic research clinicians and investigators representing cognitive, social, and personality psychology.

Configurational analysis is a step-by-step approach to the description of human problems, resources, and processes of change and a method to organize and study these findings. Direct observation is followed by inference to explain patterns. Systematic unit microanalysis using diagrams is then done. Horowitz's theory is basically psychoanalytic, but energy theory gives way to an ego psychology that emphasizes information processing and self-representations and object representations. Emotions are not drive based but are consequences of ideation. Defenses are not processes but outcomes of control operations. Transcripts and videotapes are essential to the verification of gross and microanalytic formations.

The actual plan for configurational analysis involves three reviews, each using three modes of analysis: 1) a description of the states of the patient, 2) the patient's characteristic manner of experiencing self and others during these states, and 3) the patient's patterns of processing or avoiding information about these interpersonal situations. The first review establishes a baseline, the second explores patterns during change, and the third review is done at the designated time for outcome assessment. Horowitz precedes these nine steps with the establishment of a problem list based on the patient's complaints and the therapist's inferences.

The book centers on the demonstration of the method using a 12-session psychotherapy of a young woman who could not grieve over the sudden death of a brother. Two- and 10-month follow-ups showed continued improvement. The clinical material is three-dimensional and fortified with adequate but not plethoric transcript citation. Horowitz provides a dictionary of states of mind illustrating undermodulated, modulated, and overmodulated affective sets. Some that I found particularly expressive were "pressured dumping" as an example of undermodulated communication, "grandiose bellicosity" as an example of undermodulated anger, and "phony poignancy" as an example of overmodulated sadness. Precipitants of shifts from one state to another as well as careful descriptions of the states gathered from patient reports and empathic observation allow complex descriptions of individual patients. They also make possible wide discrimination between two patients carrying the same *DSM-III-R* diagnosis.

Horowitz studies self-concepts and role relational models by paying particular attention to motivated misapplications of inner views and episodes of ignoring the realistic properties of interpersonal situations in favor of projected personal stereotypes. Again, there is a dictionary of self-concepts and object concepts containing 52 nouns and 100 adjectives; this dictionary allows such combinations as "fooled critic," "heroic avenger," and "devoted caretaker." Interpersonal aims, intentions, and expectations include such sets of alternatives as "tenderly love, cherish," "have sex with," "lustfully possess," and "sadistically use." The work on relationship patterns assumes that everyone has many schemata, persisting and fluctuating agendas, and conscious and unconscious conflicting motives.

To Horowitz, conflict is pattern mismatch that arises during comparison of sets of ideas. Emotional processes are then the signaling system that makes known the degree and quality of discrepancy. Feelings can set off controls that, in feedback, affect the continuing process. Coping or failure to adapt then occurs. Horowitz's elaboration of what I have just described in an overly condensed fashion is necessarily convoluted. Thus, it is a pleasure to find in bold type a 10-line "Recapitulation," which includes encouragement to readers to continue their attempt to prepare "a bold statement of constellations of ideas that are either warded off or repetitively intrusive in relation to conscious thought and action" (p. 79).

Change in the patient requires change from the dominant self-concept to another preexistent self-concept or to newly integrated or developed schemata that serve as evidence of structural personality change. To assess this, Horowitz studies the therapeutic alliance and inner models of patients and therapists. Analysis of change caused by therapist interventions involves the most inferential aspects of the technique. An aberration in a specific constellation in the change period is described in terms of expression of warded-off ideas, new awareness of concepts, sequential flow of a topic, and the therapist's input that affected each transition. In Horowitz's words, "This is a tall order and needs adjustment to each individual circumstance" (p. 118). Here, as in many other places, detailed diagrams are interposed to illustrate concepts and feedback mechanisms.

Outcome is assessed, with or without follow-up interviews, by describing new states, new cycles, and their triggers and by comparing self-concepts and role relationships before therapy with those after therapy. Likewise, conflict themes are reassessed and modifications are related to changes in emotional responses, memories, and fantasies.

The last three chapters apply configurational analysis to teaching, to research, and to treatment. The appendixes pro-

vide more fleshed-out transcript illustrations. Although tough going because of its detail, this book should be read not only by the small expeditionary force of psychotherapy researchers but by the large army of therapists of every persuasion who so infrequently systematize their work with each highly individual patient.

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The Shadow of the Object: Psychoanalysis of the Unthought Known, *by Christopher Bollas. New York, Columbia University Press, 1987, 283 pp., $35.00.*

This is a book for psychiatrists who have studied some of the texts of psychoanalysis. For those familiar with the current as well as the classical theories of psychoanalysis, reading Christopher Bollas's volume can be a mind-expanding experience. Bollas is Director of Education at the Austen Riggs Center in Stockbridge, Mass., and Professor of English at the University of Massachusetts. He is a member of the British Psycho-Analytical Society, the British Association of Psychotherapists, and the Instituto di Neuropsichiatria Infantile of the University of Rome. He is a sensitive clinician, as evidenced by the accounts of his treatments in this volume. He is also a master of the different theories of contemporary psychoanalysis, especially as developed in Great Britain, and his innovative synthesis of these is most illuminating. His own newer theoretical constructions (e.g., the trisexual, normatic illness) are exciting to read and compare with one's own experiences and understanding.

The volume is divided into four broad sections: The Shadow of the Object, Moods, Countertransference, and Epilogue. In this brief review it is impossible to discuss many details; however, in the introduction the author presents the themes that unfold in the later chapters.

Along with Paula Heimann, a member of the British Psycho-Analytical Society, Bollas asks, when listening to a patient's free associations, Who is speaking? The classical assumption is that it is the patient who tells what he or she is thinking about to the analyst. But Heimann and Bollas suggest that the patient "could be speaking with the voice of the mother, or the mood of the father, or some fragmented voice of a child self either lived or withheld from life" (p. 1).

The next query is, To whom is the person speaking? According to the paradigm of transference, it may be that the patient is speaking to mother, father, or others. And the communication can convey anticipation, fear, reproach, or excitement. Furthermore, the message may be that of a child in infancy, in a separation phase at age 2, in the oedipal phase, or in adolescence. Thus, we have a communication model—the sender, the fantasies about the receiver and what he or she may respond with, and the message itself.

To be sure, the receiver also responds (even a nonresponse is a response), and this response reaction can or may influence what the patient is attempting to communicate. Margaret Little, another British psychoanalyst, suggests that the analyst should be asking what she or he is feeling in reaction to the patient, why she or he is feeling this, and why now. Thus the "dialogue" (a term that in the United States has different meanings) of transference and countertransference sets in focus "a discourse of object relating."

The continuing interplay of transference and countertransference led to the theory of projective identification, i.e., how the patient "uses the analyst as an object in the transference in order to put the analyst into the patient's mind, compelling the analyst to relive with the analysand the nature of the patient's early life and to exist with some feeling inside his internal object world" (p. 2).

As the patient regresses to earlier child experiences, the analyst empathically is with the patient. Later in the volume, Bollas discusses countertransference as empathy. Drawing on Bion, Bollas suggests that the transaction, which is linked to what is occurring and the form it takes, permits the analyst to listen to the production in terms of interpersonal object relations (e.g., mother speaking to child or child to father) as well as sensitive elements of the psyche addressing each other, like instruments in a symphony.

Even though we are dealing with an intersubjective field, we are in the intrapsychic domain. At times many repetitions take place before the full meaning of the patient's communications are understood. The logic of narrative sequence and the emphasis on the word and language have their significance, as do the emphases of Bollas, e.g., understanding the wordless elements of communication.

The early experiences fall on the ego like a shadow, leaving traces of these experiences in the adult. In other words, the shadow that is cast may not be processed through mental representations or language but still exerts its influence. The analyst, using himself or herself as an instrument, is able to make sense out of these emergences of earlier experiences that are known to the patient at a deep level but not yet thought. This is the prime subject of this book.

Bollas focuses in the first part of the book on the infant's experiences and in the second section on childhood. The third part of the book examines remembering of early experiences by the patient through the transference and countertransference. "The analysand compels the analyst to experience the patient's inner object world" by means of projective identification (p. 5). This is accomplished "by inspiring in the analyst a feeling, thought or self state that hitherto has only remained within himself" (p. 5). Bollas appreciates the difference between memories of the actual mother and the unconscious fantasies of mother. He believes psychoanalysts must distinguish between representations of the actual and of the fantasy. The mother in the transference is a composite, but one can seek to distinguish between the actual and fantasized representation. In this work, Bollas does not discuss how one might analyze the presence of the actual mother in the transference.

Bollas defines his use of such terms as "ego," "subject," and "self." These definitions are at some variance with these concepts as used by other psychoanalysts. One may agree or disagree with Bollas, but he tries to make his positions clear and known. "A very significant portion of our existence is predetermined by . . . the unthought unknown, and a psychoanalysis will bring the unthought known into thought, through the experience and the interpretation of the transference and countertransference" (p. 9). Although Bollas uses terms like "self" as if they were unities, he appreciates that there are many different self states that come and go. In some ways these self states are points of view of how we sense, feel, observe, and reflect on the separate experiences of our being. From these many vantage points, including how others experience us, we establish images of our person.

In a very forthright manner Bollas addresses complexities, how he thinks about them, how he gets his ideas, and at times how he works on an idea without knowing exactly what it is he is thinking—a very creative illustration of his work with patients as well as ideas.

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The Role of Psychoanalysis in Psychiatric Education: Past, Present, and Future, *edited by Sidney H. Weissman and Robert J. Thurnblad. Madison, Conn., International Universities Press, 1987, 349 pp., $30.00.*

The editors and contributors of this book are to be congratulated on its timeliness, quality, and helpfulness. After an intense 20-year period after World War II of domination by psychoanalysis, the fields of psychiatric education and practice, in frustration over the disappointments in their unrealistic expectations, turned to psychopharmacology, community mental health clinics, and behavioral and social interventions. We are now again in the throes of reevaluating disillusionments dictated by clinical reality. From an overvaluation of psychoanalysis, psychiatry turned in hopeful expectation to the more biological and "scientific" disciplines, accompanied by an emphatic rejection of the psychodynamic. In the recent past, few residency programs offered training in psychodynamic psychotherapy. More recently, in response to clinical necessity and even formal requests to their administrations from residents-in-training in some of our prestigious training programs, the place of psychoanalysis and psychoanalytic psychotherapy in training programs and in practice is being reassessed.

This book consists of 13 chapters by relevant authorities and editorial comments by Weissman. The quality of the chapters is generally excellent; some are outstanding. The problem is that just as psychiatry evolved over the past 40 years, so has psychoanalysis. Now there is no longer a single psychoanalytic doctrine to be placed neatly in a training context. Psychoanalysis is in the throes of its own fundamental changes. It, too, is deemphasizing its century-old biological roots and finds itself convulsively but eagerly trying to establish more "experience-near" frames of reference (1). Currently there are several vigorous schools of psychoanalysis that time will test.

When the dust settles, there will be a viable, reenergized psychoanalysis and psychoanalytically based psychotherapy for residency training directors to put proportionately in place alongside the biological and social interventions. Customized decisions will have to be made as to how much and what type of psychoanalysis and psychotherapy will be taught, which residents should have how much psychoanalytic training to develop their psychotherapeutic skills, when personal psychotherapy and/or psychoanalysis is indicated for the individual resident, what the place of the new psychoanalyses is in consultation-liaison programs, and how all this will influence child psychiatry training. Rather than an emphasis on retrospective genetic psychodynamic reconstructions, there will also be a need for research and training on prospective human development as influenced by the accidents of life.

The timeliness of this book is highlighted by suggestive evidence that recent changes in criteria for medical school admission result in a student population with more interest in psychiatric and psychodynamic training.

This is a fine book. It is recommended heartily to teachers and students of psychiatry and psychoanalysis and also to all those who enjoy maintaining a perspective on the paths of current development in these two vigorous and growing fields.

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The Many Faces of Shame, *edited by Donald L. Nathanson. New York, Guilford Press, 1987, 370 pp., $30.00.*

Guilt, the hallmark of psychoneurotic character problems, is probably the most thoroughly studied emotion and the most effectively treated symptom in psychoanalysis and dynamic psychotherapy. However, as every experienced therapist knows, we are much more likely to encounter shame than guilt in our patients, to say nothing of ourselves. *The Many Faces of Shame,* a clinically oriented collection of essays on the nature and treatment of this ubiquitous but ill-defined affect, is both welcome and timely.

Excellent as most of the individual contributions to this book are, they are not well integrated—in spite of the editor's valiant efforts to do so by means of a preface to each piece. This is not unexpected, given the fact that shame is still a relatively unexplored subject, a condition which this book is trying to correct. Even more to the point, the study of shame is hampered by the widely held misconception that there is as yet no comprehensive theory of affective life in general. Although it is not its main purpose, this book does a great deal to correct that misapprehension.

In this review I will indicate how I would have liked to approach this collection and how its many readers may get the most out of it. (I hope that there will be many readers.)

Otto Allen Will, Jr., gives an overview of the experience and appearance of shame at different age levels; this overview provides a good introduction to the subject (pp. 309–314).

The editor's introduction to the chapter written by Silvan S. Tomkins rightly credits Tomkins with creating the field of modern affect study. On the basis of Darwin's work, Tomkins established the presence of a "hardwired" set of basic affective responses that serve as the foundation for the infant's communication with the mother and other caregivers. However, most of the contributors to this volume seem not to be aware of Tomkins's seminal work, around which their individual contributions could profitably have been organized. This lack of awareness accounts for the often frustrating lack of cohesion among the different chapters in this book. Fortunately, Tomkins (pp. 137–144) takes the time to briefly but effectively review the basic premise of his theory, namely, that affect is initially a response to the intensity and shape of stimulation. This explains how infants—obviously incapable of analyzing their experiences conceptually—can nevertheless accurately both encode and communicate the

qualitative nature of what is happening to them at any given time.

Nathanson, in the first of his two contributions to this volume, provides a clarifying review of Tomkins's affect theory as a setting for his comprehensive and eminently comprehensible review of the vicissitudes of shame throughout human maturation (pp. 1–50). With this as background, the reader is able to integrate the more specific contributions made by the other authors.

Leon Wurmser illustrates and discusses three forms of shame: "shame anxiety, shame affect as a complex reaction pattern, and shame as preventive attitude" (p. 68). His discussion of defense against shame (p. 86) calls attention to what is probably the most common, the most neglected, and the most important task that psychotherapists face, i.e., the shame of shame. It is the shame about revealing their shame that prevents so many patients from cooperating with their therapists, even when they are well aware that it is in their best interest to be as revealing about themselves as they possibly can be. The therapist's failure to recognize and/or work empathically with patients' shame about their shame accounts for many of the failures and impasses in insight psychotherapy.

The late Helen Block Lewis, a pioneer in the investigation of shame, takes as her thesis and illustrates clinically that "the phenomena of shame are at the root of the behavior and symptoms of many so-called 'narcissistic' or 'borderline' personalities" (p. 94). Her differentiation between the experiences of the emotions of shame and guilt are especially valuable for the clinician.

Carl D. Schneider discusses shame and the need for privacy and makes the case that "a mature sense of shame functions to prevent us from shaming others" (p. 205). The therapist's potential for breaking the barrier of privacy and shaming the patient is discussed cogently in the context of the need to maintain therapeutic tact throughout the course of treatment. As Schneider puts it, "Correct interpretations are not necessarily good interpretations" (p. 208).

Using extensive clinical examples, Warren Kinston demonstrates that " 'the capacity for shame' is as crucial as the 'capacity for concern (guilt)' " (p. 244).

In his second essay, "Shaming Systems in Couples, Families, and Institutions," Donald Nathanson shows how one's experience of shame prepares the way for using shaming as a weapon in interpersonal conflict.

Andrew Morrison equates shame with Kohut's concept of "selfobject" failure. Morrison considers shame to be the intrapsychic marker of defects in the self—thus adding the necessary psychoanalytic input clarifying the effects of shame on the formation of psychic structure and how these may be dealt with in therapy.

Robert J. Stoller, in his inimitable fashion, discusses the connection between shame and excitement in the daydream—drawing on the widespread interest in pornography for his clinical examples.

This book has succeeded in bringing together a number of very important contributions regarding the phenomenology and dynamics of shame, the clinical significance of that affect, and the technique for approaching it therapeutically. It can be read profitably by even the experienced therapist, can be used to good advantage by the teacher of psychotherapy, and is a must for the student in the field.

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PSYCHOPHARMACOLOGY

Psychopharmacology: The Third Generation of Progress, *edited by Herbert Y. Meltzer, M.D. New York, Raven Press, 1987, 1,705 pp., $150.00.*

This book is the updated edition of the classic psychopharmacology texts published under the auspices of the American College of Neuropsychopharmacology (1, 2). The large scope of the work is made manageable by masterful editing, this time by Dr. Herbert Meltzer. Each of the 184 chapters is a relatively brief discussion of a given topic with a specific focus and is not intended to be an encyclopedic review. Enough overview is given, however, to place the topic in context, and adequate referencing is included to guide the interested reader further. Through these topical chapters and the references listed, the reader is introduced to all of modern psychopharmacology.

The book is divided into three sections: Basic Neurobiology, Biological Psychiatry, and Clinical Psychopharmacology. Many advances in these broad areas made this edition necessary, and the focus throughout is on current research, especially in molecular biology. In the Basic Neurobiology section, emphasis is given to new findings concerning the excitatory amino acids and the neuropeptides, and the role for neurotoxins in understanding pathophysiology is reviewed. Although few clinically useful drugs are available to target these neural systems, it is clear that they play important roles in mental illness. Increased understanding of normal brain processes and pathophysiology of mental illness has resulted from the study of these systems. Despite the many new topics, there remain some areas of neuropsychopharmacology that are central to understanding drug action and mental illness. "Traditional" topics such as the function of adrenergic systems in tricyclic activity and affective illness are included. Adrenergic systems are also discussed in theories of anxiety and schizophrenia, illustrating the multifaceted role for this network (as well as all others). The questions being asked concerning norepinephrine have reached a new level of sophistication. Simplistic ideas of a single chemical and nuclei controlling a behavioral output have been left behind. Multiple receptor subtypes and second messenger interactions raise the complexity of neurotransmission an order of magnitude, and the book reflects this sophistication.

The Biological Psychiatry section includes chapters reviewing the roles of different transmitter systems in affective disorder, schizophrenia, disorders of childhood, dementia, and anxiety. Indoleamines, catecholamines, peptides, and cholinergic systems are fairly and thoroughly evaluated in most of these chapters. Somewhat disappointing is the lack of discussion of γ-aminobutyric acid (GABA) in affective disorders and glutamate in schizophrenia. Almost no mention is made of purinergic systems, which may be important neuromodulators of more "classical" neurotransmitters. Viral and immune hypotheses of schizophrenia are reviewed, and brief overviews of anatomical and functional imaging in schizophrenia are included, although these topics may be somewhat outside the province of this book. Likewise, reviews of genetic studies in affective disorders, schizophrenia, and Alzheimer's disease, although well written, might have been deleted to allow expansion of neuropsychopharmacological topics. However, the subjects are certainly germane to biological psychiatry, so they do not appear out of place.

The Clinical Psychopharmacology section takes up half the book and includes timely and pertinent discussions of

research design, statistics, and Food and Drug Administration regulations as well as the expected reviews of all major drug classes affecting mental illness and cognitive processing. Subsections are devoted to pharmacotherapy of major mental illness, pharmacokinetics, pharmacological manipulation of normal CNS functions, and drug side effects. There are many interesting and enlightening chapters dealing with drugs of abuse. This section is clearly oriented to human applications; animal data, while included, could be expanded substantially, although limits must be applied to keep the volume to a reasonable length.

It is easy to be enthusiastic about this volume. The organization of the book into three logical sections with selected topics within sections allows the reader not only to focus on a general area of interest but also to review diverse subjects. The authors are the best the field has to offer. The writing is excellent throughout, reflecting the high quality of the authors. The vast majority of contributors come from within the American College of Neuropsychopharmacology, and most reside in North America (fewer than 25 of the 271 contributors list non-North-American addresses). This volume will be the standard text for this rapidly expanding, fascinating field. Every reader familiar with the second edition (2), which should include a majority of neuroscientists and psychiatrists, will need this updated edition. It is required for every library of neurobiology, psychopharmacology, and biological psychiatry as a standard reference. It will be useful to, and read by, basic and clinical neuroscientists throughout the world. Psychopharmacology has much to offer our understanding of the brain, and this book offers much understanding, along with a lifetime of researchable questions.

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Clinical Pharmacology in Psychiatry: Selectivity in Psychotropic Drug Action—Promises or Problems? *edited by S.G. Dahl, L.F. Gram, S.M. Paul, and W.Z. Potter. New York, Springer-Verlag, 1987, 281 pp., $53.90.*

It is with some trepidation that I review a symposium proceedings. Too often such works are disjointed and uneven. The current selection is a pleasant surprise and provides a useful introduction to current research in pharmacology for the clinician as well as an update for the researcher.

The keys to the success of the work are the introductory chapters. In particular, Marshall's first chapter provides the definitions and background necessary for the naive to understand the more technical chapters to follow. Two other introductory chapters on peptides and tricyclics provide more in-depth background in stepwise learning increments that eventually lead the reader to what is necessary to understand the rest of the book. If one does not like these chapters, it is probably not worth the time to go further.

However, if one works on through the book there is a wealth of technical information about the molecular basis of action of all common classes of psychotropics. The major subsections are on anxiolytics, antidepressants, and neuroleptics. The antianxiety chapters review actions of classic and atypical compounds. In addition to covering molecular modeling, the book also covers pharmacokinetic and pharmacodynamic material, which is quite useful in understanding the actions of, for example, the benzodiazepines. These are well covered in a chapter by Greenblatt, Friedman, and Shader.

The antidepressant chapters are equally interesting. These cover all the relevant receptor systems (e.g., adrenergic, serotonergic, and γ-aminobutyric acid [GABA]). The chapter on pharmacokinetics by Gram et al. from Denmark provides a critical and fresh perspective to an area that has been covered in a number of reviews.

A particularly interesting work among the chapters on neuroleptics is that of Meltzer, who reviews issues related to negative symptoms and treatment. Unfortunately, given that there are 31 chapters in a 270-page book, not all subjects can be covered in depth. This is seen in the chapter on neuroleptic levels, which cites only a selection of the articles available. Comparison of such chapters with definitive works such as that of Baldessarini et al. (1) recently published in the *Archives* highlights this limitation.

Despite these limitations of space this work is a relevant publication both for the researcher and the clinician. I particularly recommend it to the clinician who tries to keep up with the literature and wants to expand his or her knowledge beyond what is available in standard clinically oriented reviews.

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The Psychopharmacology and Treatment of Schizophrenia: British Association for Psychopharmacology Monograph 8, *edited by P.B. Bradley and S.R. Hirsch. New York, Oxford University Press, 1986, 441 pp., $69.00.*

In this fast-paced world of rapid developments in psychopharmacology and biological psychiatry, it is sometimes necessary to pause and reflect on what we know, what we have recently learned, and what we still do not know. The present monograph, written as part of a series of reviews in psychopharmacology at the behest of the British Association of Psychopharmacology, provides just such a review. Keeping the topic of psychopharmacology in focus, the editors have divided the book into three themes. The first is a review of basic pharmacology of antipsychotic drugs as well as the neurochemistry of schizophrenia. These early chapters discuss the accumulated pharmacological knowledge of the dopamine systems as well as the chemistry of different drugs that have been used to treat schizophrenia. Another early chapter by Steven Curry (the only non-British author in this volume) is a superb review of the basic psychopharmacology of neuroleptic drugs. The neurochemistry of schizophrenia is also reviewed in chapters on animal-model neurotransmitter hypotheses. There is a good deal of overlap of information in these chapters, as one expects in a multiauthored volume,

but the information presented twice tends to reinforce itself rather than disconcert the reader. The early chapters conclude with an outstanding review of the diagnostic criteria that have been developed for schizophrenia. The reader comes to appreciate that the concept of schizophrenia is still a "working model" rather than a definitive diagnostic entity with well-validated and highly reliable components.

Three chapters by Dr. Hirsch and colleagues form the second main theme, an introduction to the fundamental concepts in research design. These chapters present an extraordinarily lucid and easily understood review of such concepts as statistical reasoning, type 1 and type 2 errors, power analysis and sample size, confidence intervals, interim analysis, and clinical trials. The reader is then led through an extremely accessible discussion of rating scales, reliability, validity, and potential sources of error. These chapters should be required reading for any psychiatric researcher, not only in the field of schizophrenia but in other psychiatric disorders as well.

The third theme, presented in the remaining chapters, focuses on the drug treatment of schizophrenia. The literature on the therapeutic and toxic effects of neuroleptics is exhaustively presented. If there is any weakness in this otherwise superb volume, it is that these chapters on treatment were written around 1984 for publication in 1985 and therefore do not include more recent data on new drugs, neuroleptic augmentation, and heterogeneity of response.

Overall, this is an excellent basic reference volume. It is recommended primarily for those who conduct research in schizophrenia, for those who are clinical psychopharmacologists, and for those academicians who teach psychopharmacology to students and residents.

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Psychosocial Aspects of Nonresponse to Antidepressant Drugs, *edited by Uriel Halbreich, M.D., and S. Shalom Feinberg, M.D. Washington, D.C., American Psychiatric Press, 1986, 109 pp., $12.00 (paper).*

This text is the 30th monograph in the American Psychiatric Press's Clinical Insights series. The book is divided into seven chapters that characterize affectively ill patients who do not respond to antidepressant medication according to operational definitions, prevalence, nosology, treatment compliance, psychosocial predictors of nonresponse, and reevaluation of the nonresponding patient.

The first chapter, although only two pages in length, is remarkably important because it lists operational definitions for the often debated nonresponse terminology. The more controversial and clinically useful of these definitions include treatment-refractory depression, significant depressive symptoms, partial response, adequate dose, and adequate length of treatment.

The next chapter reviews a total of 28 studies in an attempt to determine prevalence statistics for nonresponse. First, two studies 15 years apart suggested that 30%–35% of patients do not respond to initial treatment with a tricyclic antidepressant. However, when therapies such as ECT or lithium augmentation are subsequently used, the prevalence figure for truly nonresponsive patients is estimated to range between 8% and 10%. To achieve this 90%–92% response rate patients ought to receive at least 75% of the manufacturer's recommended maximal dose for at least 5–6 consecutive weeks.

Akiskal's discussion is an excellent characterization of different presentations of nonresponding patients and the optimal pharmacotherapy for each. Akiskal recommends different regimens for chronically dysphoric patients with either major depression, characterologic dysthymia, subaffective dysthymia, anxious depression, or "double depression."

The chapter discussing a study of the value of inpatient family intervention therapy as an adjunct to antidepressant drug therapy generates one very interesting finding. Female patients appear to benefit from family therapy in terms of both drug compliance and outcome, but male patients actually do worse when given this adjunctive treatment.

Buckley's chapter points out that the physician-patient relationship can substantially affect medication compliance. He makes a number of psychotherapeutic recommendations that the clinician may employ to help improve medication compliance.

Using data from the National Institute of Mental Health's Collaborative Program on the Psychobiology of Depression, the next chapter attempts to delineate those psychosocial factors which predict chronicity in depressed patients. Of all the factors studied (sociodemographic factors, personality, somatic treatments, life events, social role, and social support), only the personality trait of neuroticism was able to predict chronicity.

The final chapter is an overview of recent views on the definition of what factors constitute refractoriness. The authors suggest that too often patients are designated as refractory before their depression has been subtyped. Proper subtyping ultimately leads to the indication of a different somatic treatment as the treatment of choice. Additionally, it is pointed out that an inadequate response to somatic treatment is in many cases a result of inadequate antidepressant dosing and inappropriately short trials of medication. Finally, the diagnostic utility of the EEG with computerized spectral wave analysis is considered. Data are presented suggesting that refractory patients with abnormal EEGs may respond to anticonvulsants such as carbamazepine and valproic acid.

Although a relatively short monograph, this text has a number of clinically significant chapters. The data presented in these chapters should lead practitioners to rethink their diagnostic subtyping of depression, which in turn would result in a change in their somatic treatment approaches of depression.

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LAW AND ETHICS

Involuntary Civil Commitment of the Mentally Ill in the Post-Reform Era, *by Robert D. Miller. Springfield, Ill., Charles C Thomas, 1987, 257 pp., $42.50.*

Robert D. Miller outlines the legal reforms of the late 1960s and early 1970s and discusses their effects on the practice of involuntary commitment, the character of the inpatient and outpatient mentally ill populations, and the general organization of public mental health services. These issues are important in view of the trend in many parts of the

country (most notably New York City) to make it easier to commit the mentally ill for involuntary treatment.

Two particularly important legal reforms of the late 1960s and 1970s were the shift in the basis of commitment from need for treatment to dangerousness and the establishment of the patient's right to adversarial counsel. Miller argues that after these reforms "clinical criteria virtually disappeared from the legal decision-making process. Persons committed began to be characterized more by their dangerousness than by their amenability to treatment" (p. 38). As "the proportion of treatable patients declined, it became even more difficult to provide effective treatment" (p. 38).

On the basis of the evidence presented in this book, I cannot determine how (or even whether) these reforms affected the outcome of commitment decisions, the character of patient populations, or the quality of care. This difficulty is rooted in factors that are to a large extent beyond the author's control. First, as Miller acknowledges, it is impossible to isolate the effects of commitment reform from the clinical, social, political, and economic pressures to deinstitutionalize. Second, the research studies that Miller had to review are largely microanalyses; that is, most researchers have studied the effects of legal reforms on one hospital within a city or one city within a state. In addition, differences in research methods, in social and economic characteristics of study sites, in statutes across jurisdictions, and in investigators' ideological biases make it impossible for Miller to draw convincing conclusions.

Although it is clear that Miller has reviewed thoroughly the involuntary civil commitment literature, it is also clear that the research in this area is of low quality. In fact, Miller inadvertently confirms Paul Appelbaum's assessment of civil commitment research: "We can say almost nothing with certainty about the effects of massive changes in civil commitment policy of the 1970s" (1). Miller's book does tell us a lot about how research studies on civil commitment have been typically designed—by isolated individuals or research teams lacking a larger purpose. A narrow goal—to determine whether the number of commitments has increased or decreased—seems to guide most researchers. Few persons seem interested in how commitment laws have affected the mentally ill. (For clear and penetrating analyses of the shortcomings of involuntary commitment research, I recommend the series of articles published in the December 1985 issue of *Law, Medicine, and Health Care.*)

The lack of systematic research to evaluate and guide commitment policy is not a new phenomenon. Miller describes the type of information that has historically guided shifts in commitment policy: dramatic cases and emotion-laden, unsubstantiated theory. In the last set of reforms (in the 1970s) this type of information undermined the efficacy of clinically defined mental disorder and the need for treatment as criteria for commitment. Notwithstanding the need for reform, should the works of Rosenhan (2), Szasz, and Ennis have been so influential in supporting the basis for change from need for treatment to dangerousness? By extension, should the visibility of the homeless become the basis for relaxing the dangerousness standard and for encouraging the use of a relatively new and untested treatment modality—involuntary outpatient commitment? (At least two questions need to be answered about the homeless: 1) What portion of the homeless are mentally ill? 2) What portion of the homeless are members of the expanding "underclass"—the hard-core unemployable individuals who previously could have been pulled into the work force because there were a large number of unskilled manufacturing jobs? Since these jobs have moved overseas, these individuals cannot work at even minimum-wage service jobs because they lack interaction skills and are unable to meet the standards of appearance required for such work.)

Miller urges clinicians to assume an active role in shaping the character of new reforms, particularly in the area of outpatient commitment. He suggests that clinicians provide information to assist policy makers in formulating the best possible system of reform, that they monitor the clinical effectiveness of commitment programs, and that they provide relevant data to policy makers on an ongoing basis. That clinicians need to assume an active role in shaping and evaluating commitment policy is axiomatic. On the other hand, if clinicians do not have systematic information, can they expect policy makers to take their ideas seriously?

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Insanity: The Idea and Its Consequences, *by Thomas Szasz. New York, John Wiley & Sons, 1987, 397 pp., $17.95.*

There are basically two, not necessarily mutually exclusive, categories of good books. There are books that deal with important subjects and books that are enjoyable to read. This one does not fall squarely into either category. Its most notable characteristic is that it reads like a tabloid. There is a heavy reliance on inflammatory language and derogation with little true scholarly content. Ironically, Dr. Szasz's writing style is also dogmatic, which is what he criticizes in psychiatric thinking. Adopting a dogmatic style is not the most effective way of dealing with dogmatism.

The introduction is subtitled "What This Book Is About" and contains most of the basic ideas of the book: 1) mental illness does not exist, 2) psychiatry is evil, 3) mental illness is a convenient concept for society, and 4) Dr. Szasz is against psychiatry and the concept of mental illness. These are, with the exception of the problem of mental illness and responsibility, the basic ideas of the book. All of these are potentially interesting. However, Szasz deals with the ideas unidimensionally by attacking the ways that society currently works rather than developing his points in any way that would engage a reader who is looking for something more than a polemic against psychiatry.

An example of the type of unidimensional approach that characterizes the book is found in the introduction and concerns the concept of a mental disease:

> While distressing behavior is real enough, and while it is possible to describe it more or less accurately, neither that reality nor its mapping has much to do with mental illness or psychiatry. (p. 5)

Szasz correctly states that distressing behavior, which is referred to in psychiatry as mental disease or disorder, can be more or less accurately described. However, in chapter one he proceeds to assert that, because we cannot find pathological lesions for schizophrenia, it lacks the status of a dis-

ease such as cancer. This idea is not discussed with any objective scholarly rigor. What Szasz does instead is to adopt the stance that since schizophrenia cannot be defined by a lesion, it is not a disease and, furthermore, is not real. This stance raises at least two issues. In the first place, a well-worn path in science is ignored. Concepts are commonly chosen as objects of study and intervention before the achievement of a level of understanding that allows the identification of an omnipresent physical correlate having a very low degree of measurement error. This has led to important advances in many fields in addition to medicine. In the second place, there are physical manifestations, such as neuropathological abnormalities, minor physical anomalies, and neurological signs, that do correlate at different levels with the prevalence of a diagnosis of schizophrenia.

The idea that schizophrenia does not exist or at least is not properly in the domain of psychiatry may be worth considering, but accepting the idea that the entity exists as a problem only if it is defined as a problem by society suggests that it might be made nonexistent. It seems to me that if we all decide to take Szasz at his word and declare schizophrenia nonexistent, there may be some ramifications that bear discussion. Alternatives and ramifications, however, are not typically dealt with in *Insanity*.

The stylistic problem described here characterizes the entire book. The reader who is looking for an adventure in critical evaluation of basic problems in mental health will not find it in *Insanity*. Szasz makes no apparent attempt to present a balanced argument so that readers can form their own opinions. It seems that all that can be learned from reading the book are the opinions of the author. This is unfortunate, because Szasz attempts to address basic assumptions in mental health, and basic assumptions in science should always be critically examined. This is particularly true in mental health, where claims of actual knowledge about efficacy or etiology are so often overstated.

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Divided Staffs, Divided Selves: A Case Approach to Mental Health Ethics, *by Stanley Joel Reiser, Harold J. Bursztajn, Paul S. Appelbaum, and Thomas G. Gutheil. New York, Cambridge University Press, 1987, 141 pp., $25.95; $8.95 (paper).*

This book tries to add to the short list of useful books on psychiatric ethics. In my opinion, it adds very little. Hypothetical cases take up more than half of the text, and each case is followed by questions (but no answers): What should be done? What if the patient were dangerous? What if you had a drug that might cure the patient but also might kill the patient? The examples provide considerable food for thought because they demonstrate how ethical decisions have to be made in a wider range of situations than any one reader is likely to think of.

Unfortunately, the conjectural cases run to the esoteric, although not unknown, while scarcely touching on the central ethical dilemmas that trouble every profession, including the mental health professions. Most important, the examples include very few in which the psychiatrist's personal interests conflict with those of the patient or other parties. The cases would be more useful if they included more problems of the sort that psychiatrists face every day. For example, is it ethical to admit a chronically ill patient to an expensive private hospital if the psychiatrist knows of no effective treatment and is aware that the financial resources of the patient and the family will be exhausted in a few weeks? Should a psychiatrist accept a handsome fee from a pharmaceutical manufacturer to test an experimental drug if he or she strongly suspects that reporting too many untoward effects will mean no invitations to do similar studies in the future? These types of garden-variety ethical problems in which mental health professionals must weigh their personal interests against professional responsibilities are neglected, and their absence impairs the usefulness of the book.

The longest of the three short chapters that make up the remainder of the book attempts a "comparative anatomy" of mental health ethics. The authors summarize the ideas of five philosophers, then infer what each sage would have said about ethics in an actual psychiatric case. This exercise was ill-fated. Aristotle, Hegel, and J.S. Mill are expounded in two paragraphs each, Kant and G.E. Moore in one. The result is rather like summing up the writings of Sigmund Freud and Benjamin Rush in one page, then inferring from the summaries that one would have favored the father and the other the mother in a particular child custody dispute.

The definitive work on ethics in psychiatry has yet to be written. Meanwhile, readers will be better served by traditional books such as those by Block and Chodoff (1), Rosenbaum (2), and Tancredi and Slaby (3).

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The Biology of Moral Systems, *by Richard D. Alexander. Hawthorne, N.Y., Aldine de Gruyter, 1987, 280 pp., $34.95; $16.95 (paper).*

This was an extraordinarily difficult book for me to read and to review. While reading the book, I recognized how taxing it must be for a business person to read social science literature. The technical terms are different, and, even more important, one starts with no basic theoretical framework on which to hang complex and complicated ideas. I struggled through *The Biology of Moral Systems* during the New Year's period, and my first New Year's resolution was to reread this book. I hoped that perhaps a second reading would not only be more enjoyable but also allow me to understand, use, and perhaps even contest some of this distinguished author's thinking.

Richard D. Alexander is Donald Ward Tinkle Professor of Evolutionary Biology at the University of Michigan. He has written extensively on entomology, evolutionary biology, and animal behavior. *The Biology of Moral Systems* is part of a natural progression of his research and teaching, which has led him to the conviction that "our ability as a species to resolve moral and ethical problems will be aided significantly by aspects of self-knowledge that biology alone can provide." Dr. Alexander begins his thesis with an articulate

and thoughtful discussion of the seriousness of the current world crises. He believes that the accelerating technological alteration of our environment and our social structures, the depletion of the world's resources, an interest among the more powerful nations in manipulating and competing over those less powerful who possess the scarce resources the powerful nations need, and, finally, the proliferation of terrible weapons and the shrinking of the social brain that controls them have all contributed to a societal crisis of unprecedented magnitude. I agree.

Dr. Alexander says, "It may be appropriate to characterize the so-called great nations of the world today as the most enormous, most awesomely-weaponed, smallest-brained 'dinosaurs' of all time." He next states that although the ethical and moral dilemmas of our time cannot be quickly and easily solved, he believes that philosophers, politicians, theologians, psychologists, and psychiatrists who grapple over issues of morality, ethics, and justice have left one articulate point of view out of their thinking. That is the point of view of the biologist and particularly that of the evolutionary biologist. It is his hope to add that point of view to the debate, and, in fact, the body of this book does so.

Dr. Alexander develops a general theory of human interests using senescence and effort theory from biology to help analyze the patterning of human lifetimes. He then views moral questions arising from conflicts of interests. He describes moral systems as systems of indirect reciprocity in which humans gain and lose socially (and reproductively), not only by direct transactions but also by the reputations they develop in everyday social interactions. He articulates clearly, it seems to me, that the ultimate aim of society is reproductive, and the ultimate goal is to promote survival of the individual's genetic materials through descendants and through nondescendant relatives as well. If that is the case, it is obvious that the arms race is contrary to the interests of evolutionary biology, biologists, and humans, since it has the potential in one fell swoop to destroy our children and our children's children.

In his final chapter, Dr. Alexander proposes strategies for a partial stoppage of or brake on the arms race. He begins by saying, "Because I believe that, in general, people behave as they do because it is [or has been] in their [evolutionary] interests to do so, I also believe that world peace is likely to be achieved only by making it too costly for aggression to proceed." He suggests that this is how moral systems have always operated, i.e., by considering expense or cost-benefit ratio. It follows that it is too expensive to be selfish in the face of severe extrinsic threats. He suggests the following partial brakes on the arms race.

The first brake would be the perception that the effects of military spending may themselves make a nation more vulnerable to the very threats such spending is intended to offset. Dr. Alexander suggests that those who may lose by increased military spending (for example, the poor and basic science researchers in nonmilitary research) will be effective in applying this brake. The second brake comes into effect only when the threat of massive destruction becomes so great that individuals begin to see the original source of their security (their own government and its efforts to achieve national security) as a greater threat to the safety of themselves, their relatives, and their friends. (Dr. Alexander notes that the recent peace movement has been an example of the second brake.) The third brake is in effect when those controlling the use of weaponry come to realize that its use by only one side is likely to devastate both sides. He suggests that we have already reached this stage, that neither great power will be untouched if one side begins a nuclear conflagration. He suggests that "everyone will lose big and equally." The fourth brake takes effect as the realization spreads that powerful nations can destroy one another in retaliation (in a sense, this is similar to the third brake). The fifth brake involves increased communication and empathy and less secrecy and deception among world powers.

In summary, this treatise combines concepts of philosophy and biology with a somewhat difficult writing style. However, I agree with some of Dr. Alexander's conclusions. That is, humans are unique in that they have "so controlled their environments that virtually the only significant hostile force of nature affecting them now is other humans. Only humans play competitively, group against group. Only in humans are war and other forms of intergroup competition the central aspects and driving forces of social existence. Only humans have embarked on a virtually unchecked arms race involving cooperative efforts of millions of individuals on opposing sides." However, Dr. Alexander ends on an optimistic note: "We humans differ only in our ability to comprehend and reflect upon them [our lives] and to change how we feel about them" and, I would add, to change how we behave.

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TEXTBOOKS

Principles of Medical Psychiatry, *edited by Alan Stoudemire, M.D., and Barry Fogel, M.D. Orlando, Fla., Grune & Stratton (Harcourt Brace Jovanovich) (Philadelphia, W.B. Saunders Co., distributor), 1987, 692 pp., $79.00.*

Psychiatrists frequently receive announcements for new books. They may sometimes be overwhelmed by the number of new publications on different topics and may often ask themselves, "Should I buy this book?" If you have received announcements concerning the *Principles of Medical Psychiatry,* I strongly urge you to purchase this wonderful text. Drs. Alan Stoudemire and Barry Fogel have produced a first-rate book that identifies the boundaries and future directions for medical psychiatry, which, they say, "defines the medical specialist who assumes primary clinical responsibility for the diagnosis and treatment of psychiatric disorders within the medically ill population." As the editors indicate in their introduction, patients need not be acutely medically ill to require concomitant psychiatric and medical care. *Principles of Medical Psychiatry* should be part of the personal library of psychiatrists working in the general hospital or at academic medical centers.

The title is somewhat misleading in that the book does not restrict itself to a discussion of principles but also provides practical advice for the assessment and treatment of patients with a host of medical disorders. *Principles of Medical Psychiatry* is organized in a logical fashion. The first section contains 21 chapters that discuss general principles in the approach to diagnosis and treatment. Among the many topics covered are medical psychotherapy, psychiatric diagnosis, neurological assessment, neuropsychology, psychopharmacology, ECT, and the many major psychiatric disorders encountered in the medically ill and in different medical settings. The editors also include chapters focusing on syndromes or situations that are particularly difficult to manage: pain, intensive care unit syndromes, postsurgery psychi-

atric disorders, sleep disorders, and sexual dysfunction in the medically ill.

The second section of the book addresses specific disease categories or medical specialty areas of particular interest to the medical psychiatrist: cardiovascular disease, oncology, neurology, pulmonary disease, gastroenterology, chronic renal disease, dialysis and transplantation, connective tissue diseases, obstetrics and gynecology, endocrine disorders, and human immunodeficiency virus (HIV) infection. Finally, the last section comprises two chapters written by the editors that address the organization and development of combined medicine-psychiatry units.

In the limited space provided for this review, it would be impossible to comment on all the chapters contained in the book. However, several are particularly well written and pertinent to the clinical psychiatrist who works with medically ill patients. Dr. Fogel and Dr. David Faust have prepared an outstanding chapter entitled "Neurological Assessment, Neurodiagnostic Tests and Neuropsychology in Medical Psychiatry." They provide a "string of pearls" to assist the reader in the application of the neurological examination to psychiatric patients. They state that "many neurological disorders are diagnosable more on the basis of the history than on the basis of the examination." Their review of specific neurodiagnostic procedures used in psychiatry is particularly informative, concise, and accurate. Finally, they provide an outstanding overview that summarizes the major neuropsychological assessments used in clinical psychiatry and the uses and limitations of these tests.

Another chapter of particular note written by the editors is "Psychopharmacology in the Medically Ill." They discuss in great depth the cardiovascular effects of tricyclic antidepressants, drug interactions, doses, and plasma levels. Their summary of neuroleptics includes an excellent discussion of alternative medications that may be used to manage an agitated medically ill patient. Their summary of monoamine oxidase inhibitors (MAOIs), lithium, and benzodiazepines is clinically relevant and very helpful for understanding the possible complex drug interactions and the precautions that must be taken when using these medications in patients with different medical disorders.

Other chapters of particular note are "Dementia and Delirium" written by Drs. Andrew Slaby and Leah Cullen and "Neurology" by Dr. M. Eileen McNamara. The chapters are scholarly yet practical and present material in a very understandable fashion. Finally, two classic chapters that should be required reading for all residents are Drs. Wendy Thompson and Troy Thompson's on pulmonary disease and Dr. Thomas Wise's on gastroenterology. These three psychiatrists are well-recognized experts in their respective areas and provide a wealth of useful clinical information.

What makes this book so remarkable is the high quality of all the chapters. The editors obviously spent a great amount of time working with authors to prepare scholarly yet easily understandable chapters. Each of the contributions includes extensive bibliographies. The references are very up-to-date and include many 1986 and 1987 publications. The chapters are well organized and include many tables that residents and staff can readily turn to as questions arise. The typeface is quite large, which makes for easy reading. It is a very attractive yet compact book. The index is extensive and enables the reader to refer to particular topics among different chapters.

I agree wholeheartedly with the evaluation of Dr. Alfred M. Freedman in his foreword to this book:

> In a period in which there is a relative paucity of new clinical ideas and of methods to implement them, Drs. Stoudemire and Fogel have produced a volume that is original and creative and can serve as a catalyst not only for new ways of thinking but also for ways of practice.

Principles of Medical Psychiatry certainly fulfills these expectations. The editors have achieved national prominence in medical psychiatry through their work in establishing medical psychiatry units at Brown University (Dr. Fogel) and at Duke University and Emory University (Dr. Stoudemire). They have lectured widely on this topic and have assembled in this textbook equally prominent psychiatrists in each of the different topic areas to summarize the state of the art for the reader. If I convince readers to purchase this book, I feel I would be doing a great service to the profession. *Principles of Medical Psychiatry* is a classic and is the first, I am confident, of many editions.

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1987 Year Book of Psychiatry and Applied Mental Health, *edited by Daniel X. Freedman, M.D., Reginald S. Lourie, M.D., Med.Sc.D., Herbert Y. Meltzer, M.D., John C. Nemiah, M.D., John A. Talbott, M.D., and Herbert Weiner, M.D. Chicago, Year Book Medical Publishers, 1988, 499 pp., $42.95.*

Freud (1) considered educating, healing, and governing to be the three impossible professions. This consideration is frequently misquoted to include parenting or diplomacy (2). Certainly, Freud (3) considered psychiatry to be among the healing professions. Nonetheless, were he alive today, he likely would have added, as a separate category, a fourth impossible task: being a psychiatrist who attempts to keep up with the current psychiatric literature. The *1987 Year Book of Psychiatry and Applied Mental Health* is both a revealing metaphor of the impossibility of this task and an ingenious device by which the psychiatrist can cope with the reality of a vast avalanche of essential information.

As one volume among 34 in other subspecialty areas of medicine (from anesthesia to vascular surgery), the *1987 Year Book of Psychiatry and Applied Mental Health* uses six outstanding editors to select, review, and critically outline recently published articles from 17 subspecialty areas in the field. The topics considered are Biological Psychiatry, Genetics and Mental Health, Learning and Memory, Mental Retardation, Child and Adolescent Psychiatry, General Clinical Topics, Clinical Psychiatry, Psychosomatic Medicine, Geriatric Psychiatry, General Psychotherapy, Psychopharmacology, Psychiatric Nursing, Drug Abuse, Narcotic Addiction, Alcoholism, Law and Psychiatry, and Community Psychiatry.

More than 100 journals were considered. Remarkably, 50 journals were devoted exclusively to some aspect of psychiatry, medical psychology, or the clinical neurosciences, while the other 50 were relevant multispecialty journals (e.g., *Lancet, JAMA,* and the *New England Journal of Medicine*) and generic scientific journals that relate importantly to our field (e.g., *Science* and *Nature*). In addition, the book offers both a subject index (e.g., aging, agoraphobia, AIDS, akathisia, and akinesia), and an author index, which includes the names of all the authors of the more than several hundred papers considered in the volume. Surprisingly, within this

taut structure are refreshing variability and vitality, stemming from the ingenuity, intelligence, diversity, and cantankerousness of the editorial panel.

Each of the six experts approaches his section somewhat differently. For example, Dr. Meltzer juxtaposes three or four articles that are related in subject matter but are written by different authors and published in different journals. After each article, he provides an ingenious, succinct, and unifying paragraph. The critical summaries of all the editors bring to life either the essential contribution or the inherent frailty of the papers. For me, the net effect and benefit of the editors' commentaries are similar to that of an announcer at a sports event: even though I may have read the original article (which often was not the case), and even though the summary of the article is quite clear, the highlighting by the commentator of specific details or important global trends immeasurably enriches the experience. An example of this is Dr. Weiner's discussion of a study that appeared in *JAMA*, "Increased Antidepressant Use in Patients Prescribed Beta Blockers." This large computer-based analysis of Medicaid prescribing records for 143,353 patients examined tricyclic antidepressant (TCA) use in patients prescribed any of the commonly used antihypertensive medications. The study disclosed that TCA use was significantly higher in patients taking β-blockers (23% over a 2-year period) than in patients taking hydralazine (15%), hypoglycemics (15%), methyldopa (10%), or reserpine (10%). Thus, the data showed a higher incidence of antidepressant use among patients prescribed β-blockers than in other patients with hypertension or those with diabetes. This paper is often cited as an indication that CNS dysfunction—especially depression—may be a relatively common side effect of β-blocker use. Dr. Weiner's terse but orienting commentary on this article is:

> The implications of this study are very important but not definitive: A causal relationship between the use of β-blockers and TCAs is suggested; the implication is that the former causes depression. But it is not clear from the report whether the TCAs were given for a clinically defined depressive disorder; some physicians prescribe them for pain, panic disorders, and sleep disturbances. Thus, the study is both interesting and should act as a warning signal. But the implication that β-blockers known to have central effects are causally linked with depression is suspect.

Drs. Lourie and Freedman provide 1- or 2-page overviews before presenting summaries of the papers considered in their respective areas. It was particularly pleasing to me that mental retardation was included with a specific focus on such practical clinical issues faced by psychiatrists as dealing with self-injury and idiosyncratic responses to psychotropic medications, including paradoxical hyperactivity associated with sedative use. Dr. Freedman is effective not only in highlighting important new insights related to psychopharmacology but also in exposing crucial areas where uncertainty remains.

A particularly appealing and entertaining aspect of the *1987 Year Book of Psychiatry and Applied Mental Health* is the presentation and discussion of relatively controversial findings appearing in journals that many psychiatrists do not regularly read. For example, a paper in the journal *Drug and Alcohol Dependence* suggested that, for moderate drinkers, alcohol may provide a buffer against the effects of stress, to which Dr. Nemiah replies, "This review of the beneficial effect of the moderate ingestion of alcohol reminds us that it has its uses as well as abuses." Dr. Nemiah also provides the following:

> Alcohol abuse, for example, is increasingly viewed in the context of its relationship to other psychiatric symptoms, syndromes, and to personality disorders, and modern research continues to uncover genetic and other factors that predispose the individual to difficulty from drinking. At the same time, in this age of Neopuritanism, it is reassuring to learn from a review reported below of the clinical uses of alcohol that, imbibed in moderation: "Malt does more than Milton can to justify the ways of God to man." (p. 363)

Although useful, stimulating, and pleasurable, the *1987 Year Book* is not without its pitfalls or problems. First, although the *Year Book* series does not proclaim to review or even sample comprehensively or representatively the published literature for a single year, some readers may mistakenly draw this conclusion. The 1987 volume, for example, does not contain articles by such seminal and prolific contributors as Nancy Andreasen, Joseph Coyle, Eric Kandel, Gerald Klerman, Solomon Snyder, Robert Spitzer, Joaquim Puig-Antich, Otto Kernberg, and many, many others.

A second problem is the currency of the volume. Well over half of the summarized articles were originally published in 1985, and there is increasing competition from other modalities that may offer critiques, abstracts, and summaries of published psychiatric articles in a more timely fashion. Examples of the competition using a format similar to that of the *Year Book* series include special sections in psychiatric journals, audiotapes, and specialized journals devoted entirely to critical abstracts such as *Current Opinion in Psychiatry*.

Third, the *Year Book* format imposes the challenge of just how and for what purposes to use this book. For example, does one read it through from cover to cover in several sittings, or is it better used as a convenient, occasional reference for information about a particular area of psychiatry? Is it useful as an educational supplement for residents, or is it a helpful resource to prepare for a specialty board examination? My answer is an enthusiastic, "All of the above and more," with the added suggestion that an individual's use of this text might qualify as an ingenious projective test of his or her personality structure.

Notwithstanding these challenges, I wholeheartedly recommend the *1987 Year Book*. It is not only a unique and stimulating sampling of the published scientific literature in psychiatry but also a revealing insight into how six of our specialty's most gifted leaders view this literature and the yearly progress of our field.

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A Narrative Textbook of Psychoanalysis, *by Peter L. Giovacchini, M.D. Northvale, N.J., Jason Aronson, 1987, 371 pp., $35.00.*

Dr. Giovacchini is a practicing psychoanalyst of wide experience, a teacher, a researcher deeply devoted to his craft, and a writer of substance. This book should be read, studied, and digested. It contains clearly written and excellently organized practical and theoretical information.

The general design of the book is the comprehensive presentation of standard psychoanalytic theory and practice and then criticisms and additional comments of leaders in psychoanalysis, ego psychology, and object relations. In the debate that appears, my impression is that Freud and the author win hands down. The author notes that psychoanalysis addresses the external world, and he emphasizes that it is critical to learn classical concepts as a foundation for current and future ideas.

The book consists of four parts. The definition of psychoanalysis is developed in part one, Freud's Discovery of the Unconscious. Unlike other sciences, in psychoanalysis the method of study and the basic assumptions are emphasized rather than the study of the object, the psyche. It is a depth psychology: deterministic, clinically and biologically oriented, and developed from the amorphous id to mentational structure in relation to cultural influences. The dynamic unconscious is basic, and intrapsychic clashes are correctable through interpretation of transference in therapy.

Part two is devoted to Mapping the Unconscious. Fundamental topographic, structural, psychodynamic, and psychoeconomic hypotheses are developed, along with instinctual theory. An interesting reference is made to dreams and how impulses become pictorial expressions. The elusive type of dream, which occurs in creative minds gifted with the capacity to contact the primitive self and maintain a hold on secondary process, is mentioned. Knowing it is a dream, the sleeper permits the realization of omnipotence.

Part three addresses the Clinical Use of Psychoanalysis. Dr. Giovacchini notes that analysts are not concerned with diagnoses, although assessment is essential to determine psychoanalytic treatability. He also states that psychoanalytic treatment is limited to a small and select group of patients who can withstand its restrictions. Attention is given to primary and secondary anxiety theories and their reconciliation. Twelve defenses are arranged in hierarchical order; rationalization is first and primitive denial is last.

Part four focuses on the most controversial aspects of ego psychology and object relations; the works of Hartmann, Kernberg, and Kohut are presented. According to Dr. Giovacchini, ego psychology has not been integrated into classic psychoanalysis and some aspects of object relations are old ideas in new clothes. Fairbairn and the British school emphasized adaptation to the outer world rather than inner needs. Winnicott's transitional space receives much attention as a seat of cultural experience. Because of inevitable distortions, Dr. Giovacchini cautions against "adult-morphisms," which ascribe sophisticated reactions to infants.

It is known that the purist does not accept as psychoanalytic any psychological research that does not adhere strictly to Freudian doctrine. "Contamination" of the psychoanalytic process can occur with suggestion, empathy, and support, even in the psychoanalytic setting. Some analysts, the author notes, question whether interpretation itself is significant. The public finds psychoanalysis "too unsupportive, too abstinent, and too threatening." The common denominator of all "contaminated" psychoanalytic therapy, if successful, is, in my opinion, transference cure or flight into health. Freud (1) warned us about this, but he recommended the "gold of analysis and the copper of suggestion" for wider application of his work. Other outstanding analysts have presented accommodative modifications of psychoanalysis for the public. Does it matter so long as suffering is relieved? It does matter for scientific purposes.

In future editions of this book, I recommend that a study of the use of psychotropic medication and psychoanalysis be added along with a systematic study of the results of psychoanalysis. A useful bibliography and a workable index are included. The book has my unqualified recommendation to all mental hygiene workers, teachers, students, and the informed laity.

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The Handbook of Psychiatry, vol. 5: The Scientific Foundations of Psychiatry, *edited by Michael Shepherd. New York, Cambridge University Press, 1985, 257 pp., $65.00; $24.95 (paper).*

As Dr. Shepherd states in his foreword to the series, the purpose of the *Handbook of Psychiatry* is to "concentrate on the fabric of psychological medicine and the loom of observations and concepts on which it has been woven" (p. x). He has succeeded admirably in this task by selecting outstanding editors and contributors for each of the volumes. In addition, he edited volume 5.

In the United States, the general use of the term "handbook" implies a concise, practical, and clinically oriented book that practitioners may employ to resolve day-to-day patient management problems. The British "handbook" is just the opposite. Volume 5 and the others provide comprehensive reviews on selected topics in psychiatry. This confusion in terminology may lead to a misunderstanding of the purpose and depth of this volume and the series by U.S. psychiatrists.

The Scientific Foundations of Psychiatry contains an impressive list of contributors, representing acknowledged experts in the field from Great Britain and the United States. Nine of the 19 contributors to volume 5 are from the United States. The book is divided into four parts: Philosophy and Psychiatry; Epidemiology and Genetics in Relation to Psychiatry; Social Science, Psychology, and Ethology in Relation to Psychiatry; and The Neurosciences in Relation to Psychiatry. Each of the chapters within these sections represents scholarly and well-considered reviews of its subject. For instance, The Neurosciences in Relation to Psychiatry includes a wonderful chapter by T.J. Crow and J.F.W. Deakin entitled "Neurohumoral Transmission, Behaviour, and Mental Disorders." The chapter includes excellent figures that outline the distribution of different neurotransmitter pathways in the CNS. The authors also discuss in depth each of the major neurotransmitters of psychiatric relevance. They then relate neurochemical dysfunction to the development of selected psychiatric disorders. The other two chapters in the section,

on neuroendocrinology and neuropathology, are equally outstanding.

The 10 chapters that make up this volume are all of high quality. Although many of the books and articles cited are of British origin, the readers should find these references refreshing and a stimulating addition to their knowledge base. A common critique of multiauthored textbooks relates to the unevenness in style, content, and organization among selected authors. This is certainly not the case in this volume. The references for all the chapters (except chapter one where it is less important) are extensive and up-to-date. The book contains a list of the chapters contained in other volumes in the series. It also contains extensive cross-references on major topics for each of the volumes, an extensive author index, and an index for this current volume. Finally, this book contains a cumulative index for the entire *Handbook of Psychiatry* series.

Psychiatrists working in academic settings, those involved in research, and psychiatric residents who want to read brilliant summaries of selected topics related to the core disciplines of modern psychiatry should purchase this book. Additionally, if the other volumes are of the same high quality as this one, the entire series would be a useful addition to one's professional library. This book is clearly a modern classic that summarizes a diverse range of scientific topics of critical importance to psychiatry, from philosophy to neuropathology. The reader will be charmed with the elegance and grace with which complex material is presented in an understandable and scholarly fashion.

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FAMILIES OF THE MENTALLY ILL

Understanding Major Mental Disorder: The Contributions of Family Interaction Research, *edited by Kurt Hahlweg and Michael J. Goldstein. New York, Family Process Press, 1987, 332 pp., $30.00.*

This is a collection of research reports on how families affect patients with schizophrenia, affective disorders, and alcoholism. There is also a section on marital discord, which was included because the editors view the study of marital discord as analogous to that of the genesis and exacerbation of psychopathology by the presence of "communication deviance" and the vicissitudes of "expressed emotion" and "affective style" in patients' families. The concept of deviant communication was developed by Wynne and Singer more than 20 ago. About 10 years ago, British researchers Vaughn and Leff discovered that schizophrenic individuals who lived in a family characterized by high expressed emotion had a 9-month relapse rate three to four times that of those who lived in a family characterized by low expressed emotion. Expressed emotion has been measured in interviews with family members, and researchers assess affective style during sessions with the family, including the patient.

In their introduction, the editors review the history of family interaction research. They contend that cross-sectional studies, based on the notion that dynamic disturbances in the family could cause an illness such as schizophrenia, have failed to identify diagnosis-specific patterns of family conflict or even to distinguish patients' families from other families. Beginning about 20 years ago, researchers turned to prospective studies of high-risk families, and more recently their emphasis has been on the empirical study of family interaction variables such as expressed emotion in order to understand how and why they affect clinical course and outcome. The studies included in this volume are examples of such empirical research. The editors make it clear that workers in this field use the stress-vulnerability model of thought concerning the etiology of major mental illnesses: vulnerability is either inherited or acquired and interacts with life stress to determine the emergence and subsequent course of illness.

I compared this work with a 1965 book by Theodore Lidz and his associates at Yale (1), a collection of studies of the family environments of 17 schizophrenic patients carried out during the previous 12 years. The 17 families were intensively studied in the light of psychoanalytic theory, and many of the concepts concerning both noxious and positive family influences that are the subject of investigation in this book on family interaction research are represented in the findings, although not necessarily in the same words. This 1987 book did not contain a single reference to the 1965 book, an omission that I, as a psychoanalyst, found offensive, even though I assume it was based on the fact that the earlier work was written in the spirit of psychoanalytic hermeneutics rather than with the scientific rigor to which Hahlweg and Goldstein and their collaborators hold themselves.

What makes this new book worthwhile reading for every psychiatrist is the clear, detailed exposition of methodology, including statistical techniques. It shows us simply, in the context of several disorders, how we can understand and measure the ways in which family behavior affects a patient, how patient behavior affects the rest of the family, and how treatment interventions influence the system. The 40 contributors to this volume have developed investigative methods that allow for an important step beyond the intensive case-study method of earlier, explorative research. In other words, they have designed experiments that allow for valid scientific testing of the hypotheses generated by work such as that of the Lidz group.

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Families of the Mentally Ill: Coping and Adaptation, *edited by Agnes G. Hatfield, Ph.D., and Harriet P. Lefley, Ph.D. New York, Guilford Press, 1987, 340 pp., $40.00; $19.95 (paper).*

Probably the most potentially revolutionary development in the last 10 years of psychiatry has been the organization of the families of the mentally ill into a self-help group, the Alliance for the Mentally Ill. The goal of this group is to help patients and their families live decently and to have their mentally ill relatives recover. To accomplish these goals the Alliance engages in political activity on behalf of patients and families in order to improve the mental health care system, to foster research, and, most importantly, to keep families and patients from being scapegoated and blamed.

Families of the Mentally Ill represents one of many efforts on behalf of families of the mentally ill to present the point

of view of the family, in this case through an excellent collection of articles written by experts. A considerable number of the best chapters are by the editors themselves. This book will be of value to all mental health professionals, particularly those who work with the seriously and chronically mentally ill.

The first section of the book describes the burdens assumed by the family when there is a mentally ill member. Since the asylum function of the mental hospital is no longer funded, it is usually the family who provides safety, succor, and support. One cannot turn a mentally ill relative away from one's door, and many mentally ill individuals who need treatment are not committable. A theme running through this book is the enormous difficulty in accomplishing the task of helping such a relative and the scant aid offered by the mental health system, many mental health professionals, and the legal regulations regarding both commitment and treatment. The additional burden imposed on families by therapeutic approaches that implicitly or explicitly blame families is an important part of this burden. Indeed, much of the psychoanalytic and family therapy literature has espoused this point of view; all too often, unfortunately, the literature still maintains it. However, it is useful to remember that family therapy had its origins in the hopelessness engendered by the genetic theories of the time and the failures of the individual psychoanalytic psychotherapy used in the 1950s.

The second section of the book is devoted to a discussion of how families cope with mental illness. Here the two chapters by Terkelsen describing the family's response to mental illness and its evolution over time are outstanding. The almost inevitable loss of social supports by the families because friends and other family members usually do not understand the nature and effects of mental illness is of utmost importance. Since the Alliance for the Mentally Ill can uniquely offer peer support, understanding, and education, referral of the family to a local branch should be considered a routine part of the care of many, if not most, patients with mental illness, particularly if the patient requires considerable family support.

The final section deals with a variety of issues, including the education of mental health professionals, the new political activism of the families, and the families of the mentally ill as informed consumers. Here chapters by Bernheim and Cole are worthy of note. Important themes are the problem of the least restrictive treatment setting, important to patient advocates, as opposed to optimal treatment, advocated by the families; the inevitable concern with what will happen to the patient "after I'm gone"; and the need for family representation in the decision-making process not only with regard to their mentally ill member but, equally important, in the whole mental health system.

This collection is important, but it is not without problems, the least important of which is the fact that it is quite repetitious. In addition, this is a family advocacy book. The authors are quick and right to note any tendencies to blame families (certainly they blame themselves all too much). We mental health professionals would do well to prepare ourselves to deal with families knowledgeable about mental illness, clear about what kind of a relationship they want with a treating professional, concerned about conditions in the mental hospital, and having their own ideas about the kinds of research we should be doing. It is a bit ironic but understandable that the families support biological research when one of the contributions that led to the development of family support groups was psychoeducational groups, a product of psychosocial research.

Working with families of the mentally ill on a daily basis, one fairly quickly becomes impressed that in the end they seek and get care in the state hospital system, having used up both their health insurance and their own funds in private care, and that this system of care has the lowest prestige and pay. Working in this system one cannot but be aware of the kindness and devotion of most of the underpaid people who care for the patients and of the difficulties of their days. It should give all of us pause that the families of the mentally ill cannot go home at the end of an 8-hour day. This book speaks eloquently for them.

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Self-Help Organizations and Professional Practice, *by Thomas J. Powell. Silver Spring, Md., National Association of Social Workers, 1987, 358 pp., $16.95 (paper).*

Self-help organizations are a valuable and neglected resource for psychiatric patients in the age of rationed care. Professionals are often reluctant to make referrals to self-help programs out of ignorance, doubts about the quality and integrity of particular groups, and prejudice against ideologies that seem to encourage prolonged dependence or rigidly confirm patients' self-concepts as deviant or impaired. The time is ripe for a book that will educate the mental health professions about the benefits and limitations of self-help approaches to clinical problems and teach us how to use them as adjunctive or even primary modes of treatment.

In this book, Thomas J. Powell struggles to bridge the gap between the sometimes competing and sometimes complementary fields of self-help and professional services. The outline of his project is sound. He begins by defining the different types of self-help organizations and then analyzes the ways they help members change and grow. This leads to a systematic comparison of self-help and other types of care, followed by a scheme for classifying different self-help organizations in terms of their purpose, their modes of operation, the usual course of a member's career, and the organization's relationship to professionals. He concludes with a discussion of how professionals can collaborate with self-help systems to the benefit of all parties—the professional, the self-help organization, and the patients each hopes to serve.

Although Powell espouses a well-informed and sincere respect for nonprofessional approaches to psychosocial problems, in the end, he is the prisoner of his own professional training. He models himself on traditional sociologists, with the result that his work reads with the elegance and clarity of an Internal Revenue Service manual. Some parts of his analysis are worthwhile, such as his discussion of the benefits of self-help organizations as opposed to ad hoc or sponsored groups, or his analysis of the failure of many self-help groups to attract lower-class and minority clients. He writes from a praiseworthy ethical position, and he reminds us that self-help should be recommended for what it genuinely offers and not merely as a cheap but inadequate substitute for professional services. Unfortunately, his views are so overly abstract and turgidly expressed that only the most diligent sociology graduate student is likely to persist in the effort to understand them.

Moreover, Powell's preoccupation with sociological theory and generalization leads him to overlook some of the most difficult problems in the relationship between professionals and self-help organizations. For example, he builds a

whole theory of collaboration on reciprocal consultation between professional and self-help leaders but does not discuss how to identify the leaders of groups in which roles are fluid and egalitarian.

Although he addresses a critical issue in mental health services, the author has proven unequal to his task. Like a thin soul in a fat body, a worthwhile guide to mutually helpful collaboration between human service professionals and self-help organizations is crying out to be released from this overelaborate and poorly written book.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Interactions of Bromocriptine With Cocaine

SIR: The following case bears on recent proposals that bromocriptine may facilitate cocaine withdrawal and maintenance of abstinence in persons dependent on cocaine.

Ms. A, a 40-year-old professional woman, had started to use cocaine, along with variable amounts of alcohol, regularly when she was in her 30s. Her daily intranasal doses of cocaine averaged about 500 mg. She was medically evaluated for complaints of persistent menorrhagia, galactorrhea, and headache. She was found on CT scan to have a 14-mm pituitary tumor. In addition, her plasma prolactin was elevated to 39 mg/ml, so the dopaminergic agonist bromocriptine mesylate, 7.5 mg/day, was given. Not informed of a possible drug interaction, she continued to use cocaine and discovered that her usual daily doses were no longer effective. While taking bromocriptine, she experimented with high intranasal doses of cocaine (up to about 1500 mg) as well as inhalation of unknown large amounts of the free-base, obtaining stimulant effects but with subsequent depressant effects. Several days after bromocriptine was discontinued Ms. A found that the lower daily doses of cocaine she had used before taking bromocriptine regained their stimulant effect. Following psychiatric hospitalization, she appeared to have abstained from cocaine and alcohol for at least 6 months, although she was never free of daily craving for cocaine, even while taking 7.5 mg/day of bromocriptine.

The theoretical basis of treatment of cocaine dependence emerged largely from a "catecholamine deficiency and replacement" hypothesis suggesting that repeated use of cocaine may lead to depletion of stores or functions of cerebral catecholamines and so to symptoms of depression and craving (1), but evidence for this hypothesis remains inconclusive. We found recently (A. Campbell et al., "Bromocriptine and Cocaine Interactions: Prevention of Behavioral Arousal and Depression in the Rat," manuscript submitted for publication, 1988) that administration of bromocriptine (median effective dose=0.36 mg/kg) prevented the late behavioral depression that follows acute administration of cocaine in the rat. Unexpectedly, but similar to the case report of Ms. A, bromocriptine also antagonized the immediate stimulating effect of cocaine in the rat. As a mixed "agonist-antagonist" with limited intrinsic activity at cerebral D_2 dopaminergic receptors in the mammalian brain (2, and Campbell et al. manuscript), bromocriptine may not only substitute for the dopaminergic effect of cocaine but also compete with and, in certain conditions, actually antagonize the stimulant's CNS effects (Campbell et al. manuscript).

These observations suggest a need to modify our understanding of the interaction of bromocriptine and cocaine. Our case report appears to represent the first report of a stimulation-antagonizing, *anticocaine* action of bromocriptine in humans—an effect paralleled by dose-dependent antagonism by bromocriptine of acute behavioral stimulation by cocaine in the rat. Thus, bromocriptine may have acute anticocaine effects as well as limiting the depression and dysphoria that commonly follow use of cocaine in human beings and may contribute to further abuse. These effects may have closer parallels to the use of opioid antagonists such as naltrexone or mixed agonist-antagonists such as buprenorphine to treat heroin addiction, withdrawal, and maintenance than to the use of methadone as a substitution therapy (3). However, if the apparent antagonistic effect of bromocriptine can be surmounted by large and potentially toxic or lethal doses of cocaine, caution is appropriate in the evaluation of bromocriptine in the management of patients who abuse stimulants.

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Fluoxetine Treatment of Obsessions and Compulsions in Patients With Tourette's Syndrome

SIR: Tourette's syndrome is an inherited neuropsychiatric disorder characterized by multiform motor and phonic tics and an array of frequently associated behavioral problems, including some forms of obsessive-compulsive disorder (1). The symptoms of obsessive-compulsive disorder may be more disabling than tics, especially in older individuals with Tourette's syndrome.

Medications effective in reducing tic symptoms (e.g., pimozide, haloperidol) are of less value in treating obsessive-compulsive symptoms. Inhibitors of neuronal reuptake of serotonin, such as fluoxetine (2, 3), fluvoxamine, and clomipramine, have been shown to be useful in the treatment of "pure" obsessive-compulsive disorder. Preliminary studies (4, 5) have suggested that clomipramine ameliorates obsessive-compulsive symptoms associated with Tourette's syndrome but is less effective in reducing tic symptoms. Described here is the encouraging reduction in severity of obsessive-compulsive symptoms observed in three patients with Tourette's syndrome treated with fluoxetine.

Three white men (ages 34–37 years) were each suffering from moderate to severe Tourette's syndrome; all three also met *DSM-III-R* diagnostic criteria for obsessive-compulsive disorder. Each was receiving medication for treatment of tics (pimozide, 4 mg/day; clonidine, 0.25 mg/day; and pimozide, 6 mg/day, respectively). All three patients had been treated unsuccessfully for obsessive-compulsive symptoms with imipramine and/or desipramine; these agents were tapered and discontinued (6 months, 5 months, and 1 week, respectively) before fluoxetine treatment.

Monthly clinical assessments included self-ratings and clinician ratings for tics, obsessions and compulsions, and depression. Patients completed the Leyton Obsessional Inventory, a 68-item self-report scale that includes ratings of resistance and interference for each symptom. Following a semistructured interview, a clinician completed a battery of ratings, including a clinical global impression (CGI) for tics, a CGI for obsessive-compulsive disorder, and the Yale-Brown Obsessive Compulsive Scale.

Fluoxetine was administered for 3 months. Because of complaints of nausea, the initial dose of 20 mg/day that all three patients received was successfully reduced to 20 mg every other day for two patients. In general, the medication was well tolerated.

Marked reductions in the severity of obsessive-compulsive symptoms were observed in all three patients on all measures. Following 3 months of treatment, the mean CGI score for obsessive-compulsive disorder was reduced by 36%, the mean Yale-Brown score by 37%, and the mean Leyton inventory total score by 31%. Patients' narrative reports indicated dramatic improvement: all three reported that at no time during the past decade had they been less impaired by obsessive-compulsive symptoms.

Severity of tics, as measured on the CGI for tics, decreased 33% in one patient, increased 33% in another, and was unchanged in the third. One patient, who was clinically depressed before starting to take fluoxetine, experienced a marked and sustained reduction in depressive symptoms following 3 weeks of medication.

The three patients' mean±SD whole blood serotonin concentration level was markedly lower after 1 month (24.6±9.0 ng/ml) and 2 months (28.2±17.2 ng/ml) of fluoxetine treatment than it had been before treatment (118.0±49.0 ng/ml). It is not clear whether this peripheral effect of fluoxetine will prove to be correlated with clinical efficacy.

These preliminary results suggest that fluoxetine may be an effective treatment for obsessive-compulsive symptoms in patients with Tourette's syndrome. Controlled studies of fluoxetine in Tourette's syndrome, especially in medication-free patients, are indicated.

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Fluvoxamine in the Treatment of Panic Disorder With Obsessive-Compulsive Symptoms

SIR: The excellent article by Thomas A. Mellman, M.D., and Thomas W. Uhde, M.D. (1) suggests that the presence of obsessive-compulsive symptoms in panic disorder may predict a less favorable response to pharmacological treatment. Here we report on a patient for whom administration of fluvoxamine, a selective serotonin reuptake blocker, proved effective in amelioration of obsessive-compulsive symptoms and panic attacks.

Ms. A, a 36-year-old woman, was admitted to an inpatient psychiatric unit for treatment of panic attacks. The patient had a 12-year history of recurrent panic attacks. She met *DSM-III* criteria for panic disorder. Before her current admission, she had been treated with imipramine, up to 150 mg/day, in combination with lorazepam, up to 2.5 mg/day, for 2 months. No improvement was reported by the patient. At her admission we noted obsessive-compulsive symptoms but no symptoms of major depressive disorder or agoraphobia. After a 7-day washout period, fluvoxamine, 150 mg/day, was started. After 6 weeks of treatment, the patient experienced substantial improvement in her obsessive-compulsive symptoms and had no panic attacks.

Wise et al. (2) suggested that the serotonin system may be involved in the mediation of anxiety, and Kahn and Westenberg (3) found a beneficial effect of L-5-hydroxytryptophan, the immediate precursor of serotonin, in agoraphobia with or without panic attacks. Zimelidine, a serotonin reuptake inhibitor, has appeared to be effective in treating panic attacks (4). Fluvoxamine has been reported (5) to have some efficacy in the treatment of obsessive-compulsive disorder. In our case report, the efficacy of fluvoxamine for both panic attacks and obsessive-compulsive symptoms stresses the possibility of a shared biological mechanism in these disorders. Fluvoxamine may be an alternative treatment for patients with panic disorder and obsessive-compulsive symptoms who do not respond to usual antipanic medication.

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Neuroleptic Malignant Syndrome and Malignant Hyperthermia

SIR: Similarities in the clinical presentations of neuroleptic malignant syndrome and malignant hyperthermia suggest that these disorders may share a common pathophysiology (1, 2). Liskow (3) reported the case of a patient who received ECT soon after resolution of neuroleptic malignant syndrome. This patient tolerated without difficulty seven ECT sessions in which thiopental sodium and atracurium besylate were used during induction.

I now report a patient recovering from apparent neuroleptic malignant syndrome who experienced symptoms similar to those associated with both neuroleptic malignant syndrome and malignant hyperthermia soon after the first ECT, despite use of an anesthetic protocol (thiopental sodium and pancuronium bromide) chosen to reduce the risk of malignant hyperthermia.

Mr. A, a 22-year-old man, was admitted to a naval hospital with manic excitement. Results of his admission physical examination were normal except that he had a pulse of 120 bpm and a temperature of 38.7 °C, which rapidly normalized with rehydration. Results of routine laboratory studies were within normal limits, and results of a urine drug screen were negative. The patient received haloperidol, 20 mg i.m., during the admission process.

The day after admission Mr. A was lethargic, mute, and incontinent of urine. His temperature was 37.7 °C, his pulse was 100 bpm, and his blood pressure was 129/92 mm Hg. On day 2 of hospitalization, his vital signs again normalized, but he developed catatonia that progressed to "lead pipe rigidity." He was given amobarbital sodium, 250 mg, by slow intravenous infusion and became much more relaxed. Results of lumbar CSF examination were normal. That evening he again demonstrated manic excitement, was given chlorpromazine, 200 mg p.o., and became somnolent.

On the morning of hospital day 3, Mr. A became comatose, with a fever of 39.9 °C and a pulse of 160 bpm. There were no focal neurological findings. Results of a head CT scan were normal, and his serum creatine phosphokinase level was elevated to 7400 IU/liter. He was treated supportively for a presumptive diagnosis of neuroleptic malignant syndrome. By that evening he awoke with normal vital signs. Because he again demonstrated manic excitement on day 5, ECT was administered using intravenous thiopental sodium and pancuronium bromide, a nondepolarizing muscle relaxant. Within 6 hours after ECT, the patient's temperature increased to 39.5 °C, his pulse rose to 160 bpm, and his serum creatine phosphokinase level rose to 11,800 IU/liter. The patient was again treated supportively, and by the next day his vital signs were normal and his mental status was improved. On day 7 the results of mental status examination were normal. Mr. A started a regimen of lithium carbonate, and he remained symptom free on a therapeutic dose over the next 6 months.

This case demonstrates a similar clinical reaction to two dissimilar neuroleptic agents and subsequently to barbiturate anesthesia with pancuronium bromide muscle relaxation. The seemingly beneficial effects of amobarbital sodium during the apparent neuroleptic malignant syndrome tend to argue against thiopental sodium per se as the responsible agent. Also, barbiturates as well as pancuronium bromide appear to carry a low risk of malignant hyperthermia (4). Since the effects of neuroleptics can persist for an extended period of time after even acute doses have been stopped (5), the reaction to ECT is also complicated by the possible persistence of earlier doses of neuroleptics, independent of an anesthetic reaction. Possibly, either muscle relaxants or even a barbiturate can set off a reaction like neuroleptic malignant syndrome or malignant hyperthermia as a result of "sensitization" due to an earlier exposure to neuroleptics.

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Lorazepam for Treatment of Catatonic Symptoms and Severe Psychomotor Retardation

SIR: Sultana A. Salam, M.D., and colleagues (1) described the beneficial effect of lorazepam in patients suffering from catatonic stupor of suspected psychogenic origin. Relationships between psychogenic, neurotic, and hysterical features and catatonia-like syndromes have been discussed for a long time. At the turn of the century, in German psychiatry this discussion gave rise to concepts like *Hysterokatalepsie* and *Emotionsstupor*, which have now fallen into oblivion.

As already mentioned by Dr. Salam and associates, however, it should be emphasized that lorazepam may be useful not only in psychogenic catatonia-like states but in several catatonic syndromes of different etiology and nosological classification. Patients suffering from a malignant neuroleptic-induced syndrome (2), catatonic schizophrenia (3), and catatonic symptoms and severe psychomotor retardation associated with major affective disorder (4) showed marked improvement after administration of lorazepam. As reported previously (5), lorazepam could overcome mutism and stupor in patients with major depressive episodes (*DSM-III*) with melancholia and with mood-congruent or mood-incongruent psychotic features. It is noteworthy that this effect usually subsided when lorazepam was given alone, but it could be preserved when lorazepam was administered as an adjunct to antidepressants and/or neuroleptics in the further

course of treatment. Since lorazepam is not available for parenteral use in the Federal Republic of Germany, we have applied intravenous lormetazepam and have had success similar to that with lorazepam. Contrary to the report of McEvoy and Lohr (6), who used diazepam as an adjunct to neuroleptics, in our experience diazepam, 10 mg (either i.v. or p.o.), was not as effective as lorazepam when given to otherwise antidepressant- and neuroleptic-free depressed or schizophrenic patients with catatonic symptoms. However, because of diazepam's large distribution volume and its rapid rediffusion into peripheral compartments, high and multiple doses might be necessary.

We believe that benzodiazepines like lorazepam and lormetazepam should be given to patients suffering from stupor, mutism, and other catatonic symptoms or severe psychomotor retardation irrespective of etiological or nosological considerations, since these drugs are of both diagnostic and therapeutic value in still potentially life-threatening disorders.

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History of Phencyclidine Use and Repeated Assaults in Newly Admitted Young Schizophrenic Men

SIR: A relationship between acute phencyclidine use and aggressive behavior has been reported (1, 2). The studies exploring this relationship have been retrospective in design, have not reported reliability of the method used for the detection of the assaultive behavior, and have not focused on schizophrenic patients.

We located, within the first week after their hospital admission, a group of 79 schizophrenic men younger than 36 years of age. The patients were given a test battery consisting of a quantified neurological evaluation, drug and alcohol use questionnaires, and a psychosocial assessment. We monitored the patients' behavior prospectively for 6 months or until discharge, whichever came first, by reviewing their charts, the ward journal, and the as-needed medication records weekly. An assault was defined as the patient making physical contact with another patient or staff member. The types of physical contact included were hitting, hair pulling, kicking, pushing, scratching, and strangling. The assaults were detected reliably. The intraclass correlation coefficient (3) between the raters was 0.95.

We compared the patients who gave a history of phencyclidine (PCP) use with those who did not on demographic variables, neurological abnormality score, alcohol and other drug use, previous violence as reflected by a history of convictions for violent crime, and history of violent suicide attempts (4). Because we did not identify the patients until several days after admission, and PCP cannot be detected reliably in urine or plasma beyond 6 hours after ingestion (2), we did not attempt to corroborate the histories of PCP use by means of urine or blood samples.

Twenty-four of the 79 patients gave a history of having used PCP at least once. We found no significant differences between PCP users and nonusers with respect to time of follow-up, age, race, age at first psychiatric hospitalization, history of violent crime, neurological abnormality score, and other drug or alcohol use.

We found that the PCP users were significantly more likely to be repeatedly assaultive during the 6 months of follow-up ($\chi^2=3.65$, df=1, $p=0.05$) and to have more assaults than nonusers ($t=2.64$, df=26.9 [separate variance estimate], $p=0.05$). The PCP users also reported more violence directed toward self; they tended to report a history of violent suicide attempts more frequently than nonusers ($\chi^2=2.9$, df=1, $p=0.09$).

Our findings suggest that histories of PCP use by young, newly admitted schizophrenic men were predictive of repeated assaults in the hospital. This finding appears to be specific for PCP. Histories of alcohol use, other drug use, or violent crime were not related to assaults. The relation between a violent suicide attempt and PCP use was nonspecific.

These result are based on patients' reports of PCP use. The validity of such reports is unknown. However, we have no reason to assume that assaultive patients would be any more likely to lie about their drug histories than nonassaultive ones. Our findings, although tentative because of lack of external validation for the history of PCP use, should stimulate interest in the role of PCP in psychiatric inpatient assault.

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A Case of Psychogenic Urinary Retention

SIR: Urinary retention as a conversion symptom has received sporadic mention in the literature. Chronic urinary retention is even more uncommon, possibly because of the substantial physical distress the patient has to endure. Recently we came across a case of hysterical urinary retention that we wish to report because of the unusual nature of the presentation, although diagnosis and symptom removal posed no difficulty.

Ms. A, a 24-year-old illiterate woman who had been married for 7 years, was referred from the urology clinic of our hospital. She reported a 3-year history of not being able to pass urine unless she had coitus with her husband. Following coitus she would remain asymptomatic for 2 days before the problem started again. The period of urinary retention was associated with vague body aches, restlessness, and progressive distension of the lower abdomen. On several occasions she had not been able to pass urine for up to 3 days and had to be catheterized. Catheterization drained large volumes (up to 3 liters) of urine. There was no associated neurological deficit. Renal function tests, cystoscopy, and urodynamic studies did not reveal any pathology.

Ms. A had had a similar complaint 6 years earlier that had lasted for 1½ years and resolved spontaneously when she became pregnant. Detailed history revealed that her husband had gone away from home at that time to pursue further studies and that before the current episode he had again gone out of town to look for a job. Thus, on both occasions, Ms. A was separated from her husband before the onset of symptoms. There was no history of any extramarital relationships. The body aches and restlessness accompanying urinary retention enabled her to escape daily housework, provided her with the sympathy and attention of the entire household, caused substantial alarm, and necessitated her husband's returning home frequently.

Ms. A was admitted in our psychiatry unit and made to drink 500 ml of water every 4 hours. At the height of bladder distension, administration of a placebo tablet coupled with strong suggestion enabled her to pass urine. For the next 5 days, she passed urine without placebo but with strong suggestion. Both Ms. A and her husband were interviewed and a detailed sexual history was obtained. The therapist explained the nature of the problem to both of them. The husband was advised not to have sex with his wife when she was experiencing urinary retention. The family members were counseled not to become alarmed and not to give undue attention to Ms. A's symptom. Her husband, who had found a job, was counseled to make suitable arrangements for staying with his wife. At 6-month follow-up she continued to be asymptomatic.

Review of the literature revealed an earlier report of one case comparable to ours (1), and another report (2) described a woman who underwent surgery for urinary retention but was retrospectively diagnosed as having hysterical conversion disorder. Still another study (3) reviewed eight cases of hysterical urinary retention and noted that only 6% of the textbooks surveyed mentioned it as a conversion symptom.

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DSM-III-R Conversion Disorder and the Unconscious

SIR: *DSM-III-R* requires that a person with a diagnosis of conversion disorder be "not conscious of intentionally producing the symptom" (criterion C, p. 259). This apparent contradiction was absent from the *DSM-III* criteria for conversion disorder, which required that the symptom not be under voluntary control. The phrase "intentionally producing" means that the behavior is deliberate or purposeful, i.e., conscious. Elsewhere in *DSM-III-R*, "intentional" is used to characterize the feigned symptoms of factitious disorder or malingering, in which there is voluntary control over the symptom; this is not the case with conversion disorder.

In theory, perhaps a patient with conversion disorder could be unconscious of intentionally producing a symptom if that patient simultaneously also had multiple personality (dissociative disorder) in which one personality was unconscious of an intention and another personality was conscious of it. Notwithstanding such a rare exception, for clarity and consistency, the oxymoron of being simultaneously conscious and unconscious of the cause of a conversion symptom should be corrected in *DSM-IV*. Presumably the contradiction was *un*intentional.

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The Infant Day Care Controversy

SIR: Many parents feel guilty because they are separated from their infants and toddlers during their hours of employment away from home, often 8–10 hours a day, 5 days a week. The situation is particularly serious for those who must work to barely sustain a livelihood and who can afford only questionable child care.

As a response to this parental concern about child care, the burgeoning multibillion-dollar day care industry has attracted a variety of vested commercial, professional, and bureaucratic interests. The resulting political and commerical promotion of institutional infant day care both attracts parents away from their babies and reduces the pressure to adjust the workplace to permit parents to care for their children.

Parents need help in understanding that full-time day care is necessitated by their conventional conditions of employment, not the needs of their children. For their own social development, young children do not need full-time day care or nursery school experiences, although 3- and 4-year-olds benefit from part-time group programs.

From the clinical point of view, we know that the failure to develop attachment bonds and the substantial disruption of these emotional lifelines of infants have serious psychopathological consequences. We believe that when children are better off in day care than at home, therapeutic attention to the child-parent relationship and the child's life circumstances is indicated, rather than daily removal of the child from the parent.

We suspect that when attachment bonds are interrupted repeatedly, one of the short-range effects is an insecure parent-child relationship. This could be one reason for the widespread prescription of medications for insecure children and frustrated parents. We suspect that one of the long-range effects is the child's impaired ability to form committed relationships with other people, a factor in the alienation that underlies teen-age alcoholism, drug abuse, and suicide. To

more definitively assess these clinical impressions, we need to devote more attention to our patients' histories of delegated child care.

Numerous developmental and clinical studies of the effects of day care on children have reported both that it does and that it does not harm children. In fact, ordinary research techniques cannot answer this question. The effects of early life experience are often not evident for decades, and the problem of controlling all of the variables in child rearing invalidates anything other than large-scale experiments that could not be carried out in a democratic society.

Fortunately for us, other societies, including Israel, Czechoslovakia, and the People's Republic of China, have tested the developmental impact of institutional infant day care devised so that parents can work on a full-time basis. Even in these countries with strong commitments to the group care of children, each attempt to institutionalize infant care yielded to adjusting the workplace so that parents could care for their own babies during parenting leaves and then return to the workplace by using supplementary child care.

The challenge for parents is to balance the priorities of their families and their jobs. The priority they give to their children in early life influences the priority their children will give them in later life.

The challenge for society is to recognize the social value of parenthood and to support rather than undermine family life during this era of full-time employment of parents away from home. This can be done by recognizing the realities of parenting in the workplace, as in Scandinavia and Europe, through parenting leaves, job security, part-time employment, and child care as an extension of family life rather than a substitute for it.

The challenge for mental health professionals is to direct the attention of parents and society away from the stridency of immediate issues to the long-term needs of both parents and children.

Suggested readings on this subject can be found in references 1–5.

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Problems With Lithium Combined With ECT

SIR: Sidney Fein, M.S., M.D., and associates (1) misleadingly introduced their interesting report with the statement that "lithium combined with ECT . . . may be successful in alleviating depression." A number of case reports (reference 2, for example) and our retrospective controlled study (3) have suggested that ECT combined with lithium may be associated with complications such as severe memory loss, atypical neurological findings, and less therapeutic benefit. The National Institutes of Health-National Institute of Mental Health (NIH-NIMH) consensus statement on ECT (4) affirmed that patients who receive ECT "should be essentially lithium free."

Dr. Fein and associates cited a 25-year-old reference (5) for their assertion. However, a careful reading of that reference and the cases presented by Hartigan reveals quite clearly that he did not combine lithium with ECT in the treatment of depressed patients. He wrote, "In general the practice has been to clear up the actual depression by other means, usually electroplexy, and *then* to give lithium as prophylactic" (5, p. 812, our italics).

We suggest a mechanism relating to lithium's lowering the seizure threshold as a possible explanation for the unfavorable effects of the combination of ECT and lithium. However, a number of other mechanisms, discussion of which is beyond the scope of this letter, are also possible.

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Bulimia, Menstruation, and PMS: Treatment Implications

SIR: We read with great interest the article by Madeline M. Gladis, M.A., and B. Timothy Walsh, M.D. (1). We have also been exploring the relationship between menstruation, premenstrual syndrome (PMS), and abnormal eating behavior. In a study that followed Dalvit's findings of a daily 500-calorie increase during the 10-day interval before menses (2), we showed that women with severe PMS recorded greater premenstrual increases in calorie intake than women with mild or moderate PMS (3). Recently, we also reported the effect of menstruation on bulimia (4). Ten women meeting *DSM-III* criteria for bulimia participated in this study. All 10 reported a statistically significant increase in the total number of binge eating episodes during the 14 days before menses. All these findings suggest that bulimia can be altered by the phases of a woman's menstrual cycle.

These findings also have several practical implications for the treatment of bulimia in women. For example, if PMS increases binge eating in women suffering from bulimia, then treating the PMS first could have a positive effect on decreasing the symptoms of bulimia. We recently tested this hypothesis by following five women who met the *DSM-III-R* criteria for bulimia nervosa who also suffered from severe PMS (determined by using the *DSM-III-R* criteria for the proposed diagnosis of late luteal phase dysphoric disorder [p. 369] and Abraham's Premenstrual Distress Questionnaire). After providing informed consent, all five women were given

free medication for two menstrual cycles and asked to count their daily calorie intake and to keep daily recordings of binges. All five women showed an increase in daily binges from an average of 1.20 binges/day during days 0 through 14 to 2.60 binges/day premenstrually (days 14 through 28). There was also a corresponding calorie increase from an average of 1680 calories/day to 2335 calories/day.

All five women were then given two-cycle trials of oral micronized progesterone (300–600 mg/day during days 14–28) and placebo and asked again to record daily calorie intake and binge behavior. Conditions were double-blind and random with a crossover design. Use of all other medications was prohibited. Patients receiving progesterone recorded greater drops in premenstrual binges and calorie counts (1.60 binges/day and 1720 calories/day) than the placebo-treated group (2.40 binges/day and 2205 calories/day). No substantial side effects were reported.

These findings, although preliminary, may have several treatment implications for women who suffer from both bulimia and PMS. Whether the same holds true for women who suffer from bulimia alone remains unaddressed by this current study. We are now attempting to increase our sample size and also to include women who do not have PMS to clarify these questions.

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Medroxyprogesterone Acetate as a Treatment for Sexual Acting Out in Organic Brain Syndrome

SIR: Louis Albert Ross, M.D., and associates (1) recently described marked reduction in public masturbation and exhibitionism in an elderly mentally retarded schizophrenic male patient treated with medroxyprogesterone acetate, 200–400 mg/week, for 2 months. During treatment the patient's serum testosterone declined by 88%. His aberrant sexual behaviors returned to pretreatment levels within 1 month of stopping the drug. I have been using medroxyprogesterone acetate as a treatment for a variety of sexually disruptive behaviors in patients with dementia and mental retardation. To illustrate, four institutionalized elderly men with dementia who were masturbating in public and making inappropriate sexual overtures to female residents and who could not be managed by other means received medroxyprogesterone acetate, 100 mg/day p.o., for a 1-year trial. They were followed up for a further year. Within 2 weeks of starting the drug, the anomalous sexual behaviors had stopped; this was associated with a 90% reduction in serum testosterone levels. On stopping medroxyprogesterone acetate, testosterone promptly returned to pretrial levels in all four men; however, in three the previously disruptive sexual behaviors did not recur (2).

Continuing suppression of sexual activities has been noted with medroxyprogesterone acetate (2, 3), even in patients who have not been taking the drug for several months and whose testosterone levels have returned to normal. Apparently, this is more likely following prolonged administration and in older subjects. This could be due to continuing suppression of fantasy, which is believed to be an important ingredient of sexual arousal, or ongoing reduced sensitivity of peripheral and central androgen receptors, or it could be the consequence of antiandrogen-induced extinction of the conditioned behavioral response (e.g., the aberrant behavior) (4). However, because continuing suppression of sexual behavior (beyond the use of the drug) is unpredictable and uncertain, it has been recommended that individuals suitable for medroxyprogesterone acetate treatment receive the drug for about 2 years the first time they receive it. Then, if the recipient agrees, a decision may be made about stopping it. If this is done, the patient should be closely monitored. Any sign of relapse calls for the immediate reintroduction of the drug at former therapeutic doses (5).

Medroxyprogesterone acetate is not effective in all cases. There are reports (3) of younger subjects, most of them with pedophilia and personality disorders, who have received up to 1000 mg/week, whose sexual behaviors remained unattenuated despite a reduction in testosterone levels by up to 90%. Moreover, my associates and I (6) have described a 38-year-old sexually aggressive man with pedophilia, mental retardation, and epilepsy who was treated with 600 mg/day of medroxyprogesterone acetate for 7 months. This reduced his testosterone levels by 96%, but his sexually anomalous behaviors—measured under laboratory conditions, by using questionnaires, and by means of intensive ward observations—actually increased by 30%. Such cases appear to be rare and difficult to account for in other than idiosyncratic terms.

It has been postulated (3) that the clinical effects of medroxyprogesterone acetate are due to its capacity to lower plasma and tissue levels of testosterone below a critical level of 250 mg/100 ml. However, this is probably an oversimplification. With continuous use of medroxyprogesterone acetate, androgen levels may decline by more than 90% within 28 days. After that, however, androgen tends to go back to predrug levels without any parallel increase in sexual activities.

Probably the significance of testosterone in determining libido and sexual behaviors has been overstated. As long as a "physiological" minimum is available, the hormone may be one of a number of interdependent neurotransmitters that modulate sexual functions. Receptor sensitivity and dimensions of personality may turn out to be more important, and medroxyprogesterone acetate may have independent tranquilizing effects (5).

Despite its uncertain efficacy in suppressing anomalous sexual behavior, medroxyprogesterone acetate is safer than major tranquilizers administered for the same purpose. In my opinion, the drug should be considered as a first-line approach in the management of sexually disruptive behaviors in suitable patients with organic and functional disorders.

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Debate on the Two-Syndrome Hypothesis of Schizophrenia

SIR: Alan Breier, M.D., and associates (1) were able to prospectively demonstrate that both positive and negative symptoms of chronic schizophrenia are responsive to neuroleptic medication. Amassed in a methodologically rigorous fashion, their data reconfirmed the findings of several other researchers cited by the authors themselves. In terms of clinical import, the study generated encouragement and enhanced expectations for psychiatrists called on to treat young chronic schizophrenic patients with prominent negative symptoms. However, these data should not be considered by the casual reader as sufficient to eschew further debate on the two-syndrome hypothesis or as a demonstration of the effectiveness of neuroleptics in patients with predominantly negative symptoms. I do not believe that this was the intention of the authors.

As Andreasen (2) has pointed out, one is not likely to identify subtypes of schizophrenia unless one uses a categorical approach. Instead of focusing on the responsivity of negative and positive symptoms to neuroleptics in individual patients, researchers need to assess that variable as well as many others in the two distinct subtypes of patients in question. These subtypes should be as phenomenologically discontinuous as possible.

Dr. Breier and his associates attempted to examine the stability of positive and negative symptoms in patients during neuroleptic withdrawal and treatment phases by classifying patients into four symptom profile groups. However, their phenomenologic group corresponding to patients with relatively pure negative schizophrenia (high rating for negative and low rating for positive symptoms) was composed of only two of the 19 patients studied.

The applicability of these data to the two-syndrome hypothesis was further lessened by the relative youthfulness of the study sample (the mean±SD age was 28±8 years). In a longitudinal study, Pfohl and Winokur (3) demonstrated considerable variation in the phenomenology of schizophrenia, in that positive psychotic symptoms such as hallucinations tended to become less florid, but negative symptoms tended to become more pronounced over time. Moreover, Weinberger (4), in positing a neurodevelopmental model for the pathogenesis of schizophrenia, suggested that distinct mesocortical dysfunction (putative dopaminergic underactivity) and mesolimbic dysfunction (putative dopaminergic overactivity) account for negative and positive symptoms, respectively. In this hypothesis, normal aging appears to correlate positively with defect (negative) symptoms and negatively with positive psychotic features (5, 6). The clinical predictions of this hypothesis are readily evident in state hospital wards, in which older schizophrenic patients often manifest muted positive symptoms, appear intellectually deficient, have blunted affects, and lack logic and motivation. Neuroleptics do not seem to help these patients in any dramatic fashion. Weinberger's hypothesis applied to the youthfulness of the study sample of Dr. Breier and associates might explain why only two of the 19 patients manifested a predominantly negative symptom profile.

With these considerations in mind, more light could be shed on the two-syndrome hypothesis if two patient groups with either discrete positive or negative symptoms were evaluated in a variety of ways (for example, anatomically, physiologically, and pharmacologically) during different developmental periods in their lives. The issue of the responsivity to neuroleptics of patients with predominantly negative symptoms needs to be addressed further.

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L-Dopa for the Negative Symptoms of Schizophrenia

SIR: Readers would be well-advised to skip this letter if all the schizophrenic patients they treat are happy and function at a high level. The time invested would be wasted.

By way of introduction, several years ago I was told that I was afflicted with paranoid schizophrenia. I was told that trifluoperazine would be of help. And sure enough, positive symptoms were well-controlled by a dopamine antagonist. I was left with only one slight problem: my life was an enormous burden. Terrible, terrible negative symptoms remained. I wanted to do something. I did some research and found that L-dopa and dopamine antagonists have been used together in the treatment of the negative symptoms of schizophrenia. I found a psychiatrist willing to prescribe L-dopa. The L-dopa has been of tremendous help. I did have some serious problems when I completely stopped my dopamine antagonist. I now take 1500 mg of a combination of carbidopa and L-dopa, 1 mg of haloperidol, and one multivitamin a day. (Incidentally, I tried methylphenidate and it was not helpful.) I have not functioned this well in 15 years. I am not happy; one does not walk away, smiling, from a 15-year illness.

I do not know why the combination works. Maybe dopa-

mine receptors can be dynamically unstable—not inherently subsensitive or supersensitive, but simply unstable. Possibly, the combination of the two drugs, a dopamine agonist and a dopamine antagonist, can stabilize the sensitivity of dopamine receptor fields at an appropriate level. Possibly, a natural mechanism exists in the brain that has as one of its functions or has as its single function the control of dopamine receptor sensitivity. The two drugs together might entrain receptor sensitivity—the disastrous consequences attendant on the breakdown of the natural mechanism might be minimized by artificially regulating what the natural mechanism should control.

Something must certainly be done about negative symptoms. Basic research is absolutely essential, but L-dopa can be prescribed now. People with prominent negative symptoms have less than nothing to lose from a trial of L-dopa. With L-dopa I have hope for the first time in 15 years. I have some projects. Possibly, they will be realized.

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Dr. Andreasen Comments

SIR: As a psychiatrist who has worked with patients suffering from schizophrenia for many years, I find Mr. Berry's letter impressive. His point about the importance of finding an effective treatment for negative symptoms cannot be emphasized enough.

Several investigators have reported that L-dopa can be an effective treatment in schizophrenia (1–3). Although there are not many negative studies in print, a number of American investigators have conducted clinical trials with L-dopa and did not find it to be very effective when used as a supplement to neuroleptics. These negative studies (including one done here at the University of Iowa with a small number of patients) have tended to go unpublished. Nevertheless, it is certainly conceivable that L-dopa may be effective in some selected individual patients, and Mr. Berry appears to be an example of its effectiveness.

Mr. Berry certainly need not apologize for not understanding the mechanism of action! While early formulations of the dopamine hypothesis were relatively simple, more recently investigators have begun to consider the possibility that schizophrenia may be characterized by simultaneous deficit and excess of dopamine in different crucial brain regions (4, 5).

Fluctuations in receptor sensitivity, as suggested by Mr. Berry, are another possible explanation for the symptoms of schizophrenia and mechanisms of drug action.

All of us should be grateful to Mr. Berry for writing. Our patients teach us many things, and one of the most important is humility.

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Alcoholic Neurotoxicity in the Developing Fetus

SIR: The article by Linda A. Bennett, Ph.D., and associates (1) described several areas of reduced functioning in children of alcoholic parents. Although many of the conclusions about genetic and psychosocial contributions to these findings may be valid, the authors overlooked another important factor: alcoholic neurotoxicity in the developing fetus. The data on the children born of alcoholic mothers who were likely to be drinking during pregnancy should be analyzed separately. These children are at particular risk for deficits ranging from fetal alcohol syndrome to more modest, subtle decreases in neuropsychiatric functioning (2, 3). This group could be compared with the children of alcoholic fathers but nonalcoholic mothers. Are the study's findings still significant if data on children who had fetal alcohol exposure are eliminated from the main data analysis?

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Dr. Bennett Replies

SIR: Of the 37 alcoholic families with at least one alcoholic parent in the study, just one included a mother who was the only alcoholic parent. In this case, the mother was not drinking heavily before or at the time of the birth of the child. Therefore, a separate analysis comparing families in which the mother was alcoholic with those in which the father was alcoholic for possible fetal alcohol exposure was not justified.

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Leukoencephalopathy and Depression

SIR: H. Jordan Garber, M.D., and colleagues (1) described three patients with depressive symptoms who were noted to have high-signal-intensity lesions of the subcortical white matter on T_2-weighted brain magnetic resonance imaging (MRI). Their observations are consistent with our own investigations of the clinical and neurobiological correlates of subcortical white matter disease ("leukoencephalopathy") in depressed elderly subjects. In an early series of retrospective studies using MRI and high-resolution computed tomogra-

phy (CT), we found that leukoencephalopathy was surprisingly common in elderly patients referred for ECT and that most of these patients had late-age-onset depressive illness (2–4). These results prompted a prospective MRI study designed to investigate more formally the clinical and neuroanatomical correlates of this leukoencephalopathy.

Baseline brain MRI scans (1.5 tesla) were obtained on 52 of the 61 elderly (60 years or older) patients who received ECT during 1987 at Duke University Medical Center (our unpublished 1988 paper). Using formal rating instruments, a neuroradiologist and a neurologist-psychiatrist analyzed the MRI scans. Both were blind to the clinical interpretation of each study. Leukoencephalopathy was observed in 48 (92%) of the 52 patients and was frequently associated with cortical atrophy, ventriculomegaly, and lacunae of the brainstem and subcortical gray matter. Clinically, these patients had late-age-onset, drug-refractory depressions that responded well to ECT; patients with lacunae of the subcortical gray matter appeared to be at greater risk of post-ECT confusion. Despite extensive lesions in some patients, dementia was uncommon.

The etiology of this leukoencephalopathy remains unclear. We would agree with Dr. Garber and his associates (1) that many of the changes (at least those which are severe) are related to subcortical arteriosclerotic encephalopathy, provided other etiologies have been excluded (2–4). With milder forms of leukoencephalopathy, however, the increased T_2 signal may reflect anatomical changes (e.g., dilation of the Virchow-Robin spaces) that are commonly seen with aging (our unpublished 1988 paper). Clearly, clinicopathological studies are needed to clarify this issue.

Whatever its etiology, several lines of evidence suggest that leukoencephalopathy and related structural brain changes may have implications for the clinical phenomenology, treatment, and pathophysiology of depression, at least in some elderly patients (2–4, and our unpublished 1988 paper). Given the increased recognition of leukoencephalopathy and the frequency of depression in the elderly, psychiatrists are likely to see more patients like those described by Dr. Garber and associates and ourselves (4, and unpublished 1988 paper).

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Drs. Garber and Weilburg Reply

SIR: We find the brief report of original work by Dr. Coffey and colleagues interesting. They describe a high prevalence of white matter abnormalities detected by MRI in a population of elderly depressed patients with distinct clinical characteristics. However, it is difficult to interpret the significance of their findings. They do not report an incidence of white matter abnormalities in age-matched control groups of normal subjects or drug-responsive depressed patients. Since Dr. Coffey and his associates do not describe the neurological or medical histories of their patients, it is unclear whether risk factors for vascular pathology were present. They state that dementia was uncommon but do not say how that was determined or describe the prevalence of more subtle cognitive impairments.

Although three of the patients we reported on experienced depression, we did not propose a pathophysiology for depression that involves white matter abnormalities. Robinson et al. (1), using CT, observed a relationship between depression and poststroke lesion size and location. Similar work is needed from broader studies of depression using MRI before we can agree that there is a relationship between depression and the presence, extent, and location of white matter abnormalities.

In our article we described cognitive deficits in all four patients, which were considered possibly related to white matter abnormalities seen by MRI. We reported these cases to demonstrate a role for MRI in clinical psychiatry, not to advance hypotheses about dementia or depression. The leading perspectives on white matter abnormalities seen with MRI were summarized. These note a high prevalence in the aged and an association of risk factors for vascular disease with cognitive impairment (2).

By speculating on the pathophysiology of white matter abnormalities, Dr. Coffey and colleagues raise the interesting possibility that vascular events may not be necessary for the development of focal neuronal cell loss as visualized by MRI. They offer the Virchow-Robin space as one source for increased signal on T_2-weighted images, which we agree may be possible. The Virchow-Robin space is the cerebrospinal fluid space that surrounds pial blood vessels as they distribute into the brain substance. Loss of neural substance in the "cortical barrel" supplied by a vessel would likely produce an expansion of the interposed fluid space. The CSF therein could generate an area of prolonged T_1 and T_2 consistent with the MRI appearance of many white matter lesions without loss of an end vessel. Further work is needed to elucidate the origins of white matter abnormalities.

Investigations such as the one by Dr. Coffey and associates are innovative and appropriate applications of MRI techniques to psychiatric research. We look forward to reading a more complete report of their work.

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Treatment of Tardive Dyskinesia

SIR: I read with interest the article by George Gardos, M.D., and associates (1) on clinical forms of severe tardive dyskinesia. Although it was not meant, as I understood it, as

a review of the therapeutic strategies for tardive dyskinesia, I would like to raise some points concerning the treatment of these disabling involuntary movements. First of all, it should be emphasized that much of the tardive dyskinesia seen in patients treated with fixed doses of neuroleptics may be the result of excess medication during periods of reduced psychotic symptoms. Hence, careful clinical titration of antipsychotic medication over time, in an attempt to reduce the dose, is required. However, if, despite this, severe tardive dyskinesia develops, various therapeutic strategies have been proposed (2), depending on the clinical form of the tardive dyskinesia. In contrast to the neuroleptics used by the authors, selectively acting dopamine blocking agents (so-called D_2 receptor blockers) such as tiapride should be tried, since they have shown their beneficial effect in the treatment of choreoathetoid dyskinesia and have not been reported to induce or aggravate tardive dyskinesia itself (3).

The pathogenesis of tardive akathisia remains poorly understood. Although there is some evidence for an overactive β-adrenergic state in this form of tardive dyskinesia (4), not all patients respond well to β-adrenergic blockers. On the basis of the fact that β-adrenergic receptor subsensitivity might be induced by ECT (5), one could propose this treatment as a useful alternative when drug treatment fails (6).

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Dr. Gardos and Dr. Cole Reply

SIR: We appreciate the thoughtful comments by Dr. Deleu regarding our paper on severe tardive dyskinesia. The problems facing clinicians in treating patients with disabling degrees of dyskinesia are considerable. Established treatments are lacking. On the other hand, as we tried to demonstrate in our paper, a variety of drug combinations can be found empirically that confer benefit to a good proportion of patients. A longstanding source of frustration to workers in this field is that compounds which show promise on theoretical grounds or through animal experiments do not stand up to clinical trials. We have seen, for instance, the rise and fall of cholinergic (deanol, choline, lecithin) and GABA-ergic compounds in the treatment of tardive dyskinesia.

Dr. Deleu has specific recommendations for treating severe tardive dyskinesia. He suggests selective D_2 receptor blockers such as tiapride. This drug is not available in the United States; furthermore, we believe that while tiapride may be a promising antipsychotic with no apparent propensity to induce tardive dyskinesia, it is premature to claim superiority for selective D_2 antagonists. For instance, clozapine, which has a complex receptor affinity profile (1), is both an effective antipsychotic and a potential therapeutic agent for tardive dyskinesia, apparently without the potential to cause it (2). For tardive akathisia, Dr. Deleu recommends ECT on the basis of animal data, but we are not aware of clinical data to test this interesting idea.

Dr. Deleu decries the use of fixed doses of neuroleptics as leading to excess medication during periods of reduced psychotic symptoms and advocates clinical titration to reduce the dose. This is sound advice that astute clinicians tend to follow in the hope that research evidence will in time accumulate to validate such an approach.

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Reporting by Adult Psychiatric Patients of Childhood Sexual Abuse

SIR: In "Childhood Sexual and Physical Abuse as Factors in Adult Psychiatric Illness," Jeffrey B. Bryer, Ed.D., and associates (1) reported that 44% of a sample of 66 female psychiatric inpatients described sexual abuse before age 16. Half of those sexually victimized had been abused by family members.

In a paper now in press (2), my colleagues and I reported similar percentages. We asked about sexually stressful experiences before age 18 in a sample of 40 female inpatients. Half reported fondling or penetration; 70% of these were victims of incest.

Our data underline Dr. Bryer and associates' recommendation that patients be asked specifically about sexual abuse. In a control group of 40 female inpatients not specifically surveyed, only four (10%) voluntarily reported histories of sexual abuse. The difference was statistically significant.

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Dr. Bryer and Associates Reply

SIR: We appreciate the letter from Dr. Goodwin and colleagues reporting similar rates of childhood sexual abuse in a sample of female inpatients. Beyond the studies cited in our paper, similar findings have also come from Craine et al. (1) and Beck and van der Kolk (2).

Research reports and clinical experience continue to underscore the high rates of sexual and physical abuse among psychiatric patients. A growing body of literature strongly suggests that these traumatic experiences contribute to adult mental illness, and yet, as the data of Dr. Goodwin and colleagues confirm, few patients volunteer this information about themselves. Clinicians should ask all patients about histories of abuse. We have found that asking in the initial appointment communicates to the patient that the topic is appropriate for discussion, minimizes the more complex transference implications of asking later in an ongoing therapy, and yields valuable information as soon as possible in the evaluation process.

Two other research reports are consistent with our findings. In a study of Rorschach indicators associated with abuse, Zivney et al. (3) confirmed our finding that earlier abuse is correlated with more severe psychopathology than later abuse. Herman and Schatzow (4), in a study of the recovery and verification of memories of childhood sexual trauma, found that the majority of patients who described a history of childhood abuse could confirm through independent sources that the abuse had actually occurred.

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JEFFREY B. BRYER, ED.D.
BERNADETTE A. NELSON, PH.D.
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Philosophical Contributions to Psychiatry

SIR: I heartily agree with the analysis of Edwin R. Wallace IV, M.D., of the philosophical issues involved with the problem of certainty in contemporary society (1). I should like to add the suggestion that the basic concept of absolute truth functions as a reified wish fulfillment. There is little evidence to suggest the existence of absolute truth, any more than there is evidence to suggest the existence of a fixed future or infinite space. The stance of metaphysical realism, which assumes that reality involves only what exists "out there" and that such a reality is accessible to the mind, is a purely mental abstraction, a category of an extreme, or an extrapolation of what we can comprehend. The belief in the existence of an unchanging absolute tends to counter feelings of insecurity in a rapidly changing world. However, the subtle prevalence of such attitudes also tends to promote a fixation of one's beliefs rather than a continuation of explorations of the frontiers of knowledge.

I am concerned that the search for certainty has become an insidious, pervasive, subtle theme in modern thought and that it offers an illusory and misleading assurance. Stripped of all rationalization, it suggests that knowing "the answer" will serve as a major source of guidance. It is a projection onto science of what was once hoped for from ideal parents and then later sought from relevation. The problem is that it diverts us from what I consider the far more challenging task of creating a better world.

The alternative attitude embraces the dynamism of creativity and involves a psychosocial view of the adventure of our continuing evolution as a species. This frame of mind finds the exertions of philosophers or scientists who strive perfectionistically toward certainty to be wasteful diversions of energy. Such a goal represents an asymptotic limit, like the amount of energy it would take to move an electron at the speed of light. Instead, a creative attitude toward life can facilitate the relinquishing of what I think might be a mildly neurotic need for absolutes. This also has been the emphasis of a number of existentialist philosophers. Thus, I recommend a rereading of Dr. Wallace's paper with a self-analytical perspective, noting how the intermediate stance he has reasonably and persuasively presented invites a shift to a more courageous way of living our lives.

REFERENCE

1. Wallace ER IV: What is "truth"? some philosophical contributions to psychiatric issues. Am J Psychiatry 1988; 145:137–147

ADAM BLATNER, M.D.
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SIR: I commend Dr. Wallace (1) for his extremely well-written article on much-neglected philosophical issues in the psychiatric realm. His probing analysis and elegant historical integration of key philosophical movements in the epistemology of science is, in general, exemplary.

I share Dr. Wallace's enthusiasm, his zeal to inoculate the psychiatric community into the philosophical medium. What we do not share, however, is a common vision of what constitutes an appropriate approach for accomplishing this end. Is, for example, the *American Journal of Psychiatry* (or any medical journal) an appropriate place to "raise professional consciousness of core issues in the philosophy of science" or to mediate "between . . . rival [philosophical] points of view" (p. 137)? Do the vast majority of *Journal* readers, for example, possess the philosophical acumen necessary to evaluate the merits of arguments for "perspectival realism," "intersectional causation," or "monistic dual aspect interactionism" (2)? I suspect not. Given the complexity and subtlety of the philosophical enterprise, any attempt at imparting such skills in the context of a medical publication (given space constraints and sensitivity to the philosophical naiveté of the target audience) is less than realistic. It is not surprising, therefore, that Dr. Wallace's attempt ultimately failed. Instead of greater clarification and deeper understanding, oversimplification and obfuscation ensue.

For example, 1) Dr. Wallace freely moved between "disease" and "illness" (p. 138) as if these terms were syn-

onymous. 2) He implied that Hume assailed inductivism itself, when, in fact, a careful reading of Hume's *Treatise on Human Nature* (3) reveals that his skepticism clearly targeted the philosophical justification of inductive principles. Hume did, in fact, embrace inductivism by assumption. 3) Dr. Wallace also confounded "idealism" with "antirealism" (p. 141), and "certainty" with "veridicality" (p. 146). 4) He claimed that a "sense datum" can somehow be "transformed" into a "fact" on the basis of some apparently nonconventional renderings of these terms (p. 142). 5) He neglected Tarski's powerful theory of truth. 6) He seemed to deny that some truths can be known a priori: "We have no access to reality independent of our sensory apparatus" (p. 144). 7) He acknowledged and then ignored Thomas Kuhn and the relativity and quantum mechanical revolutions: "Our assertions must square with previous and subsequent experience" (p. 146). 8) He presented as obvious (without argument) Occam's razor, a principle that is not at all obvious and that some may say has been abandoned as a delimiter for explanation in psychodynamic theory (4). Compare this with another of Dr. Wallace's articles (2), in which he confidently proclaimed as axiomatic the falsity of metaphysical dualism. Now, although it is unclear what may or may not qualify as an axiom—or what Plantinga (5) called a "properly basic proposition"—metaphysical monism is surely an incredible candidate. Clearly, one needs to present arguments for such foundationalist assertions.

To avoid difficulties similar to those just outlined and to ensure philosophical writings of the highest quality, I advance an alternative proposal to Dr. Wallace's approach, namely, a new journal conceived specifically for these purposes, entitled, perhaps, the *Journal for the Philosophy of Psychiatry*. Persons interested in assisting with this endeavor may contact me.

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Dr. Wallace Replies

SIR: I thank Drs. Blatner and Howsepian for responding to my article. Such thoughtful letters reassure me that the article may achieve its aim—to stimulate psychiatric discussion and elaboration on philosophical issues. Because I essentially agree with Dr. Blatner, I shall focus on Dr. Howsepian's remarks. Beginning with his itemized comments in numerical order, I reserve my main point for the end.

1) His presumable reference to Kleinman's distinction between "disease" and "illness" (1) is well taken. 2) The second point, however, inserts something I did not intend. It is well-known that Hume, although philosophically skeptical about induction (and causation, too), believed us so constituted that, in effect, we *must* use such assumptions. 3) Rebutting the third point would take too much space. Suffice it to say that Berkeley (2), the prototypic modern idealist, was a realist only in deeming Divinity to be the sole reality and the phenomenal universe to be but ideas in God's mind. Schafer and Spence, I argued (pp. 141–142), *are* effectively idealist. They deny us veridical access to the patient's psychological functioning—even though they neither explicitly affirm nor deny the latter's existence.

4) In regard to the fourth point, I enunciated that "sense datum" approximates "percept" ("theory laden only in the sense in which Popper argued that all animal perception is theory laden"), while "fact" (*not* "absolute truth") is "a datum [placed] into a previously unappreciated context and novel theoretical matrix" (p. 142). 5) To make the article conform to length requirements and for clarity, reference to Tarski's linguistic rehabilitation of correspondence theory was deleted from the first draft of the paper sent to the *Journal*. 6) My essay did not address what Dr. Howsepian calls a priori "truths." I believe that induction, causality, and realism, for example, are in large measure evolutionarily acquired axioms conferring distinct adaptational advantages on their possessors. In any event, I remain unable to understand how we can have access to reality independently of our percipience, cognition, and their instrumental extensions; Dr. Howsepian seems to challenge this.

7) I oppose this point because I know of no logical or evidential compulsion to cleave either to Kuhn's brand of relativism or to acausal interpretations of quantum mechanics. Many physicists view indeterminacy as a methodological problem rather than a refutation of determinism. 8) Occam's razor ("entities are not to be multiplied beyond necessity") may not be "at all obvious," but it is a linchpin of science. It is not, as Dr. Howsepian implies, negated by the psychodynamic principle of overdetermination. Parsimonious theories are those most evidentially supported and least superfluous. Of course, if an existent, such as mind, is extraordinarily complex, then by necessity our most accurate and lapidary formulation of it must be, as well (whatever place psychoanalysis has in it) (3). In short, parsimony does not require theorems to be more simple than the actual mechanisms of their phenomena. 9) Dr. Howsepian's final criticism alludes to my mind-body essay, a companion piece published elsewhere (3). There I did precisely what he claims I omitted from the *Journal* article—thoroughly outlined the argument and distinguished among its metaphysical, epistemological, and methodological building blocks.

Above all, I oppose Dr. Howsepian's suggestion that philosophical issues are, in effect, beyond most psychiatric readers. Granted, medical journal space demands terse presentation of often difficult concepts. Nevertheless, when exemplified, esoteric ideas can become comprehensible and relevant. His proposed specialty organ might drive potentially useful philosophizing from clinical, pedagogical, and scientific periodicals. In that event, Drs. Blatner and Howsepian, myself, and others would more aptly promote an APA Committee on Philosophical Issues in Psychiatry. If, however, such a journal would not forsake interested nonphilosophical physicians, then I would readily put my shoulder to Dr. Howsepian's wheel.

Insofar as psychiatry is a clinical discipline, it relies, like all medicine, on wisdom—which is more than knowledge, which is itself more than information. This is true for both scientific and moral reasons: the former because each patient is an incredibly multivariate sentient and symbolizing organ-

ism in a particular physical, familial, sociocultural, political, and economic environment, hardly capturable by the most controlled experiments or epidemiological-statistical studies; the latter because each patient is, after all, a human being. Although psychiatry should strive to explicate and evaluate its clinical logic, basing it on the best available science, this science must be understood broadly to include all the biological, social science, and humanistic perspectives relevant to humankind in health and illness. Since science itself relies on philosophical presuppositions and axioms, and since it is unlikely that science will ever solve the big psychiatric questions such as the mind-body problem, free will versus determinism, and the moral and valuational dimensions of investigation and practice, psychiatry's most fundamental issues will belong to *philosophia*, the love of wisdom.

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DSM-III and *DSM-III-R* Dysthymia and Major Depression

SIR: In their discussion of the *DSM-III-R* criteria for dysthymia and major depression, James H. Kocsis, M.D., and Allen J. Frances, M.D. (1) wrote, "The criteria for a major depressive episode in *DSM-III-R* are essentially unchanged and, aside from depressed mood, require the presence of at least five of nine symptoms of depression." Later, the authors again wrote, "*DSM-III-R* . . . major depression requires depressed mood and five of nine symptoms." These statements are not accurate. The *DSM-III-R* criteria for major depression require either depressed mood *or* loss of interest or pleasure. Thus, depressed mood per se is not a requirement for major depression.

In contrast, depressed mood per se is required for dysthymia. It seems somewhat surprising that Drs. Kocsis and Frances did not call attention to this apparently important difference between dysthymia and major depression. It was, after all, one of the central objectives of their article to evaluate dysthymia in relation to major depression, and *DSM-III* requires depressed mood only for dysthymia.

It is not altogether obvious why *DSM-III* and *DSM-III-R* make this particular nosologic distinction and what clinical justifications exist to support its validity. In the absence of further elucidation one might speculate along the following lines in order to make meaningful the *DSM-III* distinction under discussion: in at least some clinical situations, the inability to experience positive emotion, such as interest and pleasure, reflects a more profound psychiatric disturbance than the presence of negative emotion, such as depressed mood. This seems reasonable enough because to feel no positive emotion sometimes means to be utterly detached from one's emotions. However, until the validity of this assertion is substantiated it seems appropriate to question its role in the differential diagnosis of dysthymia and major depression. The authors' comments would be appreciated.

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Drs. Kocsis and Frances Reply

SIR: Dr. Ladds has drawn attention to an interesting distinction between the *DSM-III-R* criteria for dysthymic disorder and major depression that we had not addressed in our review. In fact, the *DSM-III* criteria for dysthymia specify depressed mood *or* loss of interest or pleasure plus at least three of the associated symptoms as requirements for the diagnosis. *DSM-III* also lists loss of interest in or enjoyment of pleasurable activities and inability to respond with apparent pleasure to praise or rewards among the 13 possible associated symptoms of dysthymia. Thus, considerable weight is given to hypohedonic features in the *DSM-III* criteria for dysthymia. As far as we know, the requirement for the presence of these symptoms was removed from the *DSM-III-R* criteria for the disorder without any particular rationale.

We have accumulated data on the frequency of the different symptoms of dysthymia listed in *DSM-III*. Loss of interest in and enjoyment of pleasurable activities was the fourth most commonly reported of the 13, occurring in 57% of dysthymic patients. Because hypohedonia can occur as a chronic or perhaps even lifelong characteristic of dysthymia, it might be preferable to refer to the symptom as *lack of ability* to take interest in or to experience pleasure rather than *loss of* interest or pleasure (loss implies that the ability had previously been present).

In our critique we also noted that the *DSM-III-R* list of associated symptoms for dysthymia is overly weighted toward somatic and vegetative symptoms and that we favored retention of the broader and more cognitively oriented listing of symptoms in *DSM-III*. Lack of ability to take interest in or to experience pleasurable activities appears to be characteristic of many patients with dysthymia. We favor inclusion of this symptom among the criteria for the diagnosis.

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ALLEN J. FRANCES, M.D.
New York, N.Y.

Reprints of letters to the Editor are not available.

Highlights of the 141st Annual Meeting

The 141st annual meeting of the American Psychiatric Association was held in Montreal, Que., Canada, May 7–12, 1988. The total registration was 13,281, including 6,825 members, 2,206 spouses, other family members, and guests, 2,731 nonmember professionals, 1,236 exhibitors, 154 members of the media, and 129 staff members.

Opening Session

The opening session was called to order by George H. Pollock, M.D., 116th President of the Association, on Sunday evening, May 8, in the Montreal Convention Centre. The Honorable Therese Lavoie-Roux, Minister of Health and Social Services of the Quebec government, welcomed the participants to the meeting. Dr. Pollock then introduced the president of the Canadian Psychiatric Association, Ihsan Kapkin, M.D., and the president of the Quebec Psychiatric Society, Jean-Jacques Bourque, M.D.

Dr. Pollock recognized members of the APA Board of Trustees, members of the Executive Committee of the APA Assembly, past Presidents, past Speakers of the Assembly, past Vice-Presidents of the Association, and newly elected national and Assembly officers, Trustees, presidents of APA district branches, and chairpersons of APA councils.

Robert E. Hales, M.D., chairperson of the Scientific Program Committee, and Gaston P. Harnois, M.D., and Gilles C. Plante, M.D., co-chairpersons of the Local Arrangements Committee, were introduced and thanked by Dr. Pollock.

Dr. Pollock then introduced the following distinguished representatives of psychiatric and other related organizations from the United States and abroad:

International scholars: Prof. Jules Angst of Switzerland; Prof. Serge Lebovici of France; Prof. Sir Martin Roth of Great Britain; and Dr. Anatoly Koryagin, formerly of the Soviet Union, now living in Switzerland. (Dr. Franco Ferracuti of Italy was not able to attend.)

Representatives of other international organizations and psychiatric associations in other countries: Prof. J.J. Lopez-Ibor, Jr., Spanish Society of Psychiatry; Dr. Willem J. Schudel, Dutch Psychiatric Association; Prof. Per Vaglum, Joint Committee of Nordic Psychiatric Associations; Prof. E. Lungershausen, German Society of Psychiatry and Neurology; Dr. Chung Kyoon Lee, Korean Neuropsychiatric Association; Dr. Tan Chue Tin, Singapore Psychiatric Association; Dr. Gamal Abou El Azayem, World Federation for Mental Health; Dr. Constantine Soldatos, Hellenic Society of Psychiatry and Neurology; Prof. Michael Shepherd, Royal Society of Medicine of Great Britain; Dr. Peter Eisen, Royal Australian and New Zealand College of Psychiatrists; Dr. Eng-Kung Yeh, Society of Neurology and Psychiatry of Taiwan; Dr. Sidney Brandon, Royal College of Psychiatrists; Dr. Gustav Hofmann, Austrian Society of Neurology and Psychiatry; Dr. Clovis Martins, Department of Psychiatry of the University of Sao Paulo, Brazil; Dr. Antonio Pacheco, Venezuela Psychiatric Association; Dr. Antonio Balestrieri, Italian Psychiatric Society; Dr. William Y.K. Tam, Hong Kong Psychiatric Association; Dr. Douglas Matamoros, Psychological Association of Honduras; Dr. Sami Ibrahim El-Kari, Arab Gulf Psychiatric Association; Dr. Rodolfo Fahrer, Argentinian Society of Social Psychiatry; Dr. Ulysses Vianna Filho, Brazilian Psychiatric Association; Dr. Eli Karam, Lebanese Medical Association; Dr. Gretar Sigurbergsson, Icelandic Psychiatric Association; Dr. Jorge Costa e [illegible], World Psychiatric Association and InterAmerican Council of Psychiatric Associations; Dr. Fathy Loza, Egyptian Psychiatric Association; Dr. Morihiro Sekiyama, Japanese Association of Psychiatric [illegible]; Dr. Charles Thesiger, Caribbean Psychiatric Association; Dr. Pekka Tienari, Finnish Psychiatric Association; Dr. Ewa Bizot, Polish Psychiatric Association; Dr. Ruben J. Hernandez-Serrano [illegible], Mexican Medical Association; Dr. H.C. Raheja, Indian Psychiatric Association; Dr. Essam A. Al-Ansari, Kuwait Psychiatric Association; Dr. Zoltan Boszormenyi, Hungarian Society of Neurologists and Psychiatrists; Dr. A. Guilherme Ferreira, World Association for Social Psychiatry; Dr. Osama Al Radi, Islamic Association for Mental Health; and Dr. Paulo Alterwain, Ministry of Health of Uruguay. Dr. Pollock also recognized the Vicaria de la Solidaridad of Chile for their work with victims of torture in that country.

Representatives of organizations in the United States [illegible], President, American College of Mental Health Administration; Dr. Margaret Bean-Bayog, President, American Medical Society on Alcoholism and Other Drug Dependencies; Dr. [illegible], Secretary-Treasurer, National Council of Community Mental Health Centers; Dr. Wagner H. Bridger, President, Society of Biological Psychiatry; Dr. Ewald W. Busse, President, International Association of Gerontology; Dr. Bernard J. Carroll, President, American Psychopathological Association; Dr. Thomas [illegible], President, National Guild of Catholic Psychiatrists; Dr. [illegible] Clark, President, American Association of Community Psychiatrists; Dr. Homer C. Curtis, President, American Psychoanalytic Association; Dr. John Dluhy, President, American Society of Psychoanalytic Physicians; Ms. Suzanne Dworak-Peck, President, National Association of Social Workers; Dr. Mary Jane England, Immediate President, American Medical Women's Association; [illegible] Enzer, President-Elect, Society of Professors of Child Psychiatry; Dr. Arthur W. Epstein, Immediate Past President, American Academy of Psychoanalysis; Mr. Paul Errera, Director, Mental Health and Behavioral Sciences, Veterans Administration; Ms. Laura [illegible], Executive Director, National Alliance for the Mentally Ill; Dr. J. Frances, President, American Association of General Hospital Psychiatrists; Dr. Shervert Frazier, President, Benjamin Rush Society; Mr. E. Austin Fricker, President, Canadian Mental Health Association; Dr. Marc Galanter, Director, Association for Medical Education and Research in Substance Abuse; Dr. Kenneth D. [illegible], President, National Association of Private Psychiatric Hospitals; Dr. Robert W. Gibson, President, American Association of Medical Administrators; Dr. George Ginzberg, President, American Association of Directors of Psychiatric Residency Training; Dr. [illegible]; Dr. Kemal Goknar, President, Turkish-American Neuropsychiatric Association; Dr. Evaristo Gomez, Immediate Past President, Society of Hispanic Psychiatrists; Dr. Frederick K. Goodwin, Director-Designate, Alcohol, Drug Abuse and Mental Health Administration; Dr. Enoch Gordis, Director, National Institute on Alcohol Abuse and Alcoholism; Mrs. Katherine K. Gordon, President, American Psychiatric Association Auxiliary; Dr. A. Dale [illegible], President, Academy of Psychosomatic Medicine; Dr. [illegible], President-Elect, Black Psychiatrists of America; Dr. Jeffrey [illegible], President, Association for Academic Psychiatry; Mr. [illegible], President, National Depressive and Manic Depressive Association;

Dr. Syed Arshad Husain, President, Pakistan Psychiatric Society of America; Dr. Lewis Judd, Director, National Institute of Mental Health; Dr. Howard D. Kibel, Past President, American Group Psychotherapy Association; Dr. Edward Kingstone, President, Canadian Association of Professors of Psychiatry; Dr. L. Paul Landry, Secretary-General, Canadian Medical Association; Dr. Lawrence Lazarus, President, American Association for Geriatric Psychiatry; Dr. L. Douglas Lenkoski, President, American College of Psychoanalysts; Dr. Jerry M. Lewis, President, Group for the Advancement of Psychiatry; Dr. Richard M. Magraw, President, National Association of Veterans Administration Chiefs of Psychiatry; Dr. Leonardo C. Maguigad, President, Philippine Psychiatrists in America; Dr. Edwin P. Maynard, President-Elect, American College of Physicians; Dr. Robert Michels, President, American College of Psychiatrists, American Board of Psychiatry and Neurology, Inc. and American Association of Chairmen of Departments of Psychiatry; Dr. Sheldon I. Miller, President, American Academy of Psychiatrists in Alcoholism and Addictions; Dr. Bert Pepper, Immediate Past President, American Orthopsychiatric Association; Dr. William H. Reid, President-Elect, American Academy of Psychiatry and the Law; Dr. John J. Ring, Vice-Chairperson, Board of Trustees, American Medical Association; Brigadier Gen. James H. Rumbaugh, Representative, Surgeon General, US Army; Reverend Lucien Sawyer, President, Association of Mental Health Clergy; Dr. Charles R. Schuster, Director, National Institute on Drug Abuse; Dr. Girish V. Shah, President, American Association of Psychiatrists From India; Dr. Iradj Siassi, President, Society of Iranian Psychiatrists in North America; Dr. S. Dion Smith, President, American Society for Adolescent Psychiatry; Dr. James N. Sussex, President-Elect, Council of Medical Specialty Societies; Mr. Joseph L. Szoke, President, Association of Mental Health Administrators; Dr. Mahmoud S. Taman, Past President, Arabic-Speaking Psychiatrists of America; Dr. Gene L. Usdin, President, American Association for Social Psychiatry; Dr. Jerry M. Wiener, President, American Academy of Child and Adolescent Psychiatry.

Melvin Sabshin, M.D., introduced Dr. Pollock, who gave the Presidential Address, "Landfalls, Journeys, and Departures" (printed elsewhere in this issue of the *Journal*). L. Douglas Lenkoski, M.D., introduced Paul J. Fink, M.D., President-Elect of the Association, who gave the Response to the Presidential Address, "Is 'Biopsychosocial' the Psychiatric Shibboleth?" (printed elsewhere in this issue). Dr. Pollock then adjourned the opening session.

Business Meeting

The annual business meeting was called to order by George H. Pollock, M.D., in the Montreal Convention Centre on Monday, May 9, 1988, at 12:30 p.m.

First session. Dr. Pollock spoke in tribute to Charles Prudhomme, M.D., who died in March, and then asked the audience to observe a moment of silence in memory of all members and Fellows who died during the past year. Dorothy A. Starr, M.D., Recorder, called the roll of Assembly representatives and announced the presence of a quorum. Boyd L. Burris, M.D., chairperson of the Committee of Tellers, announced the results of the election of officers and Trustees and of balloting on amendments to the Constitution and By-Laws.

The reports to the membership followed. Each officer submitted a report to the Assembly, acting for the membership, and gave a brief summary of that report. Elissa P. Benedek, M.D., presented the Secretary's report, which was followed by the reports of Alan I. Levenson, M.D., Treasurer; Irvin M. Cohen, M.D., Speaker of the Assembly; John S. McIntyre, M.D., Speaker-Elect of the Assembly; Leigh M. Roberts, M.D., chairperson of the Committee on the Constitution and By-Laws; and John S. McIntyre, M.D., chairperson of the Membership Committee. Melvin Sabshin, M.D., presented the Medical Director's report. Reports of all the councils were also available. All reports were accepted by the Assembly as submitted and will be published in the October 1988 issue of the *American Journal of Psychiatry*.

Dr. Pollock presented the Speaker's plaque to Irvin M. Cohen, M.D., retiring Speaker, and the Vice-President's badge to Herbert Pardes, M.D., retiring Vice-President. George Tarjan, M.D., presented the President's badge to Dr. Pollock. Dr. Pollock then recessed the first session of the business meeting.

Second session. Dr. Pollock called the second session of the business meeting to order and opened the forum. The issue of continuing problems with continuity of care in the public mental health sector was discussed from the floor.

The business meeting was then adjourned by Dr. Pollock.

Convocation

The 32nd Convocation of Fellows was held in the Montreal Convention Centre beginning at 8:00 p.m. on Monday, May 9. Dr. Pollock presided. After the processional march, Dr. Pollock called the Convocation to order. The invocation was given by Edgar Draper, M.D. President-Elect Paul J. Fink, M.D., then led the ceremony conferring Life Fellowship and the induction of Fellows of the Association. Dr. Pollock introduced Distinguished Fellow René González, M.D., of San Jose, Costa Rica, and read the names of the 1987 Corresponding Fellows: Paulo Fabrykant Alterwain, M.D., Montevideo, Uruguay; Robert Henry Belmaker, M.D., Omer, Israel; Gora Chand Boral, M.D., Calcutta, India; Ajita Chakraborty, M.D., Calcutta, India; Peter Ronald Eisen, M.D., Victoria, Australia; Rodolfo David Fahrer, M.D., Buenos Aires, Argentina; and Pekka J. Tienari, M.D., Oulu, Finland. The following 50-year Life Fellows and Life Members (1938–1988) were then introduced:

Harold J. Binder, M.D., Oklahoma City, Okla.; Helen R. Burns, M.D., Compton, Calif., Jess V. Cohn, M.D., Boca Raton, Fla.; Calvin S. Drayer, M.D., Norristown, Pa.; Theodore C. Fong, M.D., Madison, Ind.; Arthur N. Foxe, M.D., Catskill, N.Y.; Emerick Friedman, M.D., Albany, N.Y.; Salomon Gagnon, M.D., Dover, Mass.; Otto L. Gericke, M.D., San Bernadino, Calif.; Helen R. Gilmore, M.D., Norwich, Vt.; Bernhardt S. Gottlieb, M.D., New York, N.Y.; John D. Griffin, M.D., Toronto, Ont., Canada; Rachel K. Gundry, M.D., Baltimore, Md.; Carl H. Hamann, M.D., Rockford, Ill.; Rafael Hernandez, M.D., Nashville, Tenn.; Edward N. Hinko, M.D., Santa Fe, N.M.; Wendell H. Hutchens, M.D., Rockaway, Ore.; Ruth E. Jaeger, M.D., Essex, Conn.; Edward Johnson, M.D., Winnipeg, Man., Canada; Douglas G. Kelling, M.D., Overland Park, Kan.; Henriette R. Klein, M.D., New York, N.Y.; Zigmond Meyer Lebensohn, M.D., Washington, D.C.; Frederick Lemere, M.D., Seattle, Wash.; William Henry McCullagh, M.D., Jacksonville, Fla.; Wrenshall A. Oliver, M.D., Napa, Calif.; Leo L. Orenstein, M.D., New York, N.Y.; Moorman P. Prosser, M.D., Oklahoma City, Okla.; Isadore Rodis, M.D., Washington, D.C.; Sidney Rose, M.D., New York, N.Y.; John A. Russell, M.D., Camarillo, Calif.; G. Lee Sandritter, M.D., Riverside, Calif.; Burtrum C. Schiele, M.D., Minneapolis, Minn.; Kathryn L. Schultz, M.D., Sykesville, Md.; Eugene L. Sielke, M.D., Vineland, N.J.; Paul Sloane, M.D., Gloucester, Mass.; Willis A. Strong, M.D., Syracuse, N.Y.; Francis J. Tartaglino, M.D., Crofton, Md.; Irving Louis Turow, M.D., Peoria, Ill.; Nicholas F. Vincent, M.D., Columbia, S.C.; Norman Westlund, M.D., Saginaw, Mich.; Alexander Wolf, M.D., New York, N.Y.; and Zuleika Yarrell, M.D., Weslaco, Tex.

Dr. Pollock introduced Anatoly Koryagin, M.D., who had been imprisoned in the Soviet Union for 6 years because of his stance against the use of psychiatry for political purposes in that country and who was released and emigrated to Switzerland last year. Dr. Koryagin gave the William C. Menninger Memorial Convocation Lecture, "Medicine Used Against Man: Psychiatry's Role."

After introducing the chairpersons of the awards committees, Dr. Pollock presented the 1988 awards. Special Presidential Commendations were presented to George L. Engel, M.D., Professor Emeritus of Psychiatry and Medicine at the University of Rochester, "in appreciation of his dedication to excellent clinical research"; to Robert E. Hales, M.D., Associate Professor of Psychiatry, Uniformed Services University of the Health Sciences, "in appreciation of his dedication to the American Psychiatric Association in his role as chairperson of the Scientific Program Committee from June 1984 through May 1988"; to Toksoz Byram Karasu, M.D., Professor and Deputy Chairman of the Department of Psychiatry of Albert Einstein College of Medicine/Montefiore Medical Center, "in appreciation of his consistent dedication and attention to the needs of psychiatry"; to Mr. Ralph C. Kelzer of Mead Johnson and Company, "in appre-

ciation of his dedication to and support of the American Psychiatric Association and of the profession of psychiatry"; to Mrs. Jeanne Robb, Director of the APA Office to Coordinate the Board and Assembly, "in appreciation of her dedication and the support she has provided to the APA officers and to the goals of the Association"; to Mr. Jerome Stone, Chairman of the Alzheimer's Disease and Related Disorders Association, "in appreciation of his dedication and outstanding work with regard to Alzheimer's and allied diseases"; and to Harold M. Visotsky, M.D., Owen L. Coon Professor and Chairman of the Department of Psychiatry and Behavioral Sciences at Northwestern University Medical School, "in appreciation of his outstanding dedication to the American Psychiatric Association and to the profession of psychiatry."

Distinguished Service Awards were presented by Dr. Pollock to Ewald W. Busse, M.D., J.P. Gibbons Professor of Psychiatry at Duke University and President of the International Association of Gerontology; to Raymond W. Waggoner, Sr., M.D., Professor and Chairman Emeritus in the Department of Psychiatry at the University of Michigan Hospitals; and to the National Alliance for the Mentally Ill, whose award was accepted by Ms. Laurie Flynn, the Executive Director. The award was established by the Trustees to honor members whose distinguished careers have ennobled the profession of psychiatry and associations that have contributed greatly to APA and its work.

Melvin Sabshin, M.D., Medical Director of APA, received the Administrative Psychiatry Award. This award honors an APA member who has served as a clinician executive in administration, excelled in the administration of major mental health programs, and served as a role model.

The APA/Pennwalt Resident Research Award, given for excellence in research undertaken during residency, was given to John H. Krystal, M.D., a postdoctoral Fellow in psychiatry at Yale University, and to Teri L. Perse, M.D., a resident in psychiatry at the University of Arizona.

Robert J. Campbell III, M.D., Director of Gracie Square Hospital in New York City and Editor-in-Chief of *Psychiatric News*, was the recipient of the Francis J. Braceland Award for Public Service, which honors a member who has made outstanding contributions as author, spokesperson, and advocate in the service of the mentally ill and disabled and to the art and science of helping them.

The Foundations' Fund Prize for Research in Psychiatry, established to recognize those who have made distinguished contributions to research in the field, was awarded to Donald F. Klein, M.D., Director of Research at the New York State Psychiatric Institute and Professor of Psychiatry at the College of Physicians and Surgeons, Columbia University.

The Samuel G. Hibbs Award was presented to Robert P. Liberman, M.D., Professor of Psychiatry in Residence at the UCLA School of Medicine. The award is given for the best unpublished paper on a clinical subject.

The Blanche F. Ittleson Award for Research in Child Psychiatry, given to a child psychiatrist or group of investigators for published results of research pertaining to the mental health of children, was presented to William R. Beardslee, M.D., a faculty scholar of the William T. Grant Foundation and Associate Professor of Psychiatry at Harvard Medical School.

Irving Philips, M.D., Professor and Director of Child and Adolescent Psychiatry at the University of California, San Francisco, received the Agnes Purcell McGavin Award, given to honor a psychiatrist who has made outstanding contributions to the prevention of mental disorders in children.

The Robert T. Morse Writers Award, which honors popular writers who have made major contributions to the public understanding of psychiatry over an extended period of time, was presented to Ms. Sandy Rovner of the *Washington Post* and Ms. Susan J. Smith of the *Rochester Times-Union*.

Oliver W. Sacks, M.D., Clinical Professor of Neurology at the Albert Einstein College of Medicine, received the Oskar Pfister Award, given to honor an individual who has made outstanding contributions to issues of mutual interest to religious leaders and psychiatrists.

The Psychiatric Institutes of America Foundation Hospital Psychiatry Research Award, given in recognition of outstanding contributions in hospital psychiatry research, was presented to three persons: Gregory R. Baumgartner, M.D., a resident in psychiatry at the University of South Carolina/William S. Hall Psychiatric Institute; Michael A. Silver, M.D., a resident in psychiatry at New York University/Bellevue Hospital; and Marvin I. Herz, M.D., Professor and Chairman of the Department of Psychiatry at the State University of New York at Buffalo School of Medicine.

Loren H. Roth, M.D., Professor of Psychiatry at the University of Pittsburgh and Director of the Law and Psychiatry Program at Western Psychiatric Institute and Clinic, received the Isaac Ray Award, presented to those who have made outstanding contributions to forensic psychiatry.

The Robert L. Robinson Award, which recognizes outstanding broadcasters whose work has significantly contributed to public understanding of psychiatry and mental illness, was given to executive producers Dan Guntzelman, Steve Marshall, and Mike Sullivan and actor Alan Thicke of the television series *Growing Pains* and to Milton Metz, host of a radio call-in program in Louisville, Ky.

The Arnold L. van Ameringen Award in Psychiatric Rehabilitation was presented to John S. Strauss, M.D., for contributions in the areas of service, research, education, and advocacy in the field of psychiatric rehabilitation and the care of the chronically mentally ill.

Richard I. Shader, M.D., Professor and Chairman of the Department of Psychiatry at Tufts University School of Medicine, was given the Seymour D. Vestermark Award, which honors outstanding contributions to undergraduate, graduate, and postgraduate medical education and to education of behavioral scientists for research in psychiatry.

The Jack Weinberg Memorial Award for Geriatric Psychiatry was presented to Franz Baro, M.D., Professor in the Faculties of Medicine, Psychology, and Law at the Katholieke Universiteit, Leuven, Belgium. The award honors a psychiatrist who has demonstrated special leadership or who has done outstanding work in clinical practice, training, or research into geriatric psychiatry.

After the presentation of these awards, Dr. Pollock adjourned the Convocation.

Awards presented at meetings other than the Convocation included the following.

The Manfred S. Guttmacher Award, given to honor outstanding contributions to the literature of forensic psychiatry, was given to Daniel W. Shuman, J.D., a member of the faculty of the Southern Methodist University School of Law.

The Jacob K. Javits Public Service Award, which honors a public servant who has made a significant contribution to the cause of the mentally ill, was received by California Assemblyman Bruce Bronzan.

District Branch Newsletter of the Year Awards were presented to the *New York County District Branch Newsletter*, Harold I. Schwartz, M.D., Editor; the *Orange County Psychiatric Society Newsletter*, Kenneth Levin, M.D., Editor; and the *Florida Psychiatric Society Newsletter*, Richard E. Gordon, M.D., Editor.

Scientific Sessions

The Scientific Program began on Monday, May 9, but Continuing Medical Education (CME) courses and industry-sponsored symposia began on Saturday, May 7. There were 16 discussion groups, 97 symposia, 20 industry-sponsored symposia, 322 new research presentations, three scientific debates, 142 papers presented in 47 paper sessions, 111 workshops (including 36 APA component presentations), 28 films, 41 videotapes, 82 CME courses, four medical updates, five reviews of psychiatry, four clinical case conferences, one continuous clinical case conference, eight "clinical consultations with . . . ," a session on Research Advances in Psychiatry: An Update for the Clinician, and an AIDS program and resource center.

There were 25 lectures. The speakers, their current positions, and the titles of their presentations are listed here.

On Monday, May 9, the following speakers gave lectures: Harry C. Holloway, M.D., Chairman of the Department of Psychiatry, Uniformed Services University, Bethesda, Md., "Psychology of Terror"; John C. Nemiah, M.D., Editor of the *American Journal of Psychiatry* and Professor Emeritus of Psychiatry at Harvard Medical School, the Adolf Meyer Lecture, "Varieties of Human Experience";

Judith Viorst, author and affiliate member of the Washington Psychoanalytic Institute, "Communication and Necessary Losses"; Prof. Sir Martin Roth, Professor Emeritus of Psychiatry at Cambridge University and Coeditor of the *British Journal of Psychiatry*, "Developments in Classification of Mental Disorders and the Scope of Biological Psychiatry"; Joel Yager, M.D., Director of Residency Education at UCLA's Neuropsychiatric Institute and the Brentwood VA Medical Center, "The Many Quests of Psychiatry: How Can the Future Fulfill Them All?"; Prof. Jules Angst, Professor of Psychiatry and head of the research department at the Psychiatric University Hospital Burghoelzli in Zurich, "Similarities and Differences Between Unipolar and Bipolar Disorders: Premorbid Personality, Course, and Outcome"; and Eva P. Lester, M.D., Professor of Psychiatry at McGill University, Montreal, "The Gender of the Therapist as a Parameter in the Transference."

On Tuesday, May 10, the following lectures were given: Melvin Sabshin, M.D., Medical Director of APA, the Administrative Psychiatry Lecture, "Administering a National Medical Association: The Joys, the Sorrows, and Other Challenges"; Frederick K. Goodwin, M.D., Scientific Director of the National Institute of Mental Health and Director of the Institute's Intramural Research Program, "Major Affective Disorders: Towards a Psychobiology of Recurrence"; Charles E. Rosenberg, Ph.D., medical historian and Professor of History at the University of Pennsylvania, the Benjamin Rush Lecture, "Body and Mind in Nineteenth-Century Medical Practice: A Clinical Context for Constructing the Neuroses"; Anatoly Koryagin, M.D., psychiatrist released last year from a Soviet prison camp, "Psychiatric Abuse in the USSR: An Update"; John R. Sladek, Jr., Ph.D., Professor and Chairman of the Department of Neurobiology and Anatomy at the University of Rochester School of Medicine, "Neural Transplantation as a Therapy for Neurologic and Psychiatric Disorders"; and Oliver W. Sacks, M.D., author and Clinical Professor of Neurology at Albert Einstein College of Medicine, the Oskar Pfister Lecture, "The Unique Case."

On Wednesday, May 11, the following lectures were presented: Prof. Serge Lebovici, Professor Emeritus of Psychiatry at the Medical School of Bobigny, University of Paris, North, "Contribution of the Psychopathological Approach of the Infant to General Psychiatry"; Richard I. Shader, M.D., Professor and Chairman of the Department of Psychiatry at Tufts University School of Medicine, the Seymour D. Vestermark Lecture, "Balance Versus Integration"; William J. Taylor, Ph.D., Vice-President for Political-Military Affairs at the Center for Strategic and International Studies in Washington, D.C., "Future of Conflict Into the Twenty-First Century"; Harvey Moldofsky, M.D., Professor of Psychiatry at the University of Toronto, "Altered Sleep in Somatoform Disorders"; Patricia Goldman-Rakic, Ph.D., Professor of Neuroscience in the section of neuroanatomy at the Yale School of Medicine, "The Prefrontal Cortex and Working Memory: The Regulation of Behavior by Ideas"; and Jeanne Spurlock, M.D., Clinical Professor of Psychiatry at the George Washington University and Howard University medical schools and Director of the APA Office of Minority and National Affairs, the Solomon Carter Fuller Lecture, "Racism Revisited."

The lectures presented on Thursday, May 12, were the following: Steven Matthysse, Ph.D., Associate Professor of Psychobiology at Harvard Medical School, "Catastrophe and Chaos in Mathematics and Psychiatry"; Arthur Caplan, Ph.D., Director of the Center for Biomedical Ethics and Professor of Philosophy and Surgery at the University of Minnesota, Minneapolis, "Redeeming Death: Ethical Issues in Organ and Tissue Transplantations"; Mordecai Richler, author and editor, "Canadian Conundrums"; Max Hernandez, M.D., psychoanalyst in private practice in Lima, Peru, the Simon Bolivar Lecture, "A Childhood Memory: Narrative, Fact, and Subjective Experience"; and Robert P. Liberman, M.D., Professor of Psychiatry in Residence at the UCLA School of Medicine, the Samuel G. Hibbs Lecture, "Training Psychiatric Patients in Social and Independent Living Skills: A Modular Approach."

Other Activities

The Committee on Local Arrangements, Gaston P. Harnois, M.D., and Gilles C. Plante, M.D., co-chairpersons, planned many activities, among which were a "fun run" and squash, tennis, and golf tournaments. A recreational bicycle ride along the Lachine Canal was arranged, and a wide choice of tours of Montreal and environs was offered. Visits to art galleries specializing in Inuit (Eskimo) art and to several museums were organized, as well as a tour of Montreal's Metro to view the art and architecture of the underground city. There were tours of Quebec City and Ottawa, excursions to the countryside around Montreal, cruises, a rafting trip, and a trout-fishing expedition. Other events included an Expos baseball game, a visit to the Stock Exchange, and a 17th-century feast at the Old Fort.

Meeting of the Board of Trustees

The Board of Trustees met in regular session on Sunday, May 8.

Meetings of the Assembly

The Assembly met on Friday, Saturday, and Sunday, May 6, 7, and 8.

ELISSA P. BENEDEK, M.D.
Secretary, American Psychiatric Association

Information for Contributors

GENERAL POLICIES

Manuscripts are accepted for consideration by the *American Journal of Psychiatry* with the understanding that they represent original material, have not been published previously, are not being considered for publication elsewhere, and have been approved by each author. Authors submitting manuscripts containing data or clinical observations already used in published papers or used in papers that are in press, submitted for publication, or to be submitted shortly should provide information on those papers to the Editor.

The requirements stated below are in accordance with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

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In addition, authors must obtain letters of permission from publishers for use of extensive quotations (more than 500 words). The *Journal* does not publish tables or figures that have appeared in another English-language publication.

Disclosure of Commercial Interests

All forms of support, including drug company support, must be acknowledged in the author's footnote (see "Acknowledgments" under the Title Page section). Also, authors must disclose in their cover letter any commercial or financial involvements that might present an appearance of a conflict of interest in connection with the submitted article, including (but not limited to) institutional or corporate affiliations not already specified in the author's footnote, paid consultancies, stock ownership or other equity interests, and patent ownership. This information will be kept confidential and will not be shared with the reviewers. Such involvements will not be grounds for automatic rejection of the manuscript. Should the article be accepted for publication, the Editor and the authors will consult on whether, and to what extent, this information should be included in the published article.

Patient Anonymity

Ethical as well as legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. In addition, authors should disguise identifying information when discussing the characteristics and personal history of patients.

Informed Consent

Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children, authors are asked to include information about whether the child's assent was obtained.

Review Process

All papers are reviewed to determine the originality, validity, and importance of content and conclusions. In addition to the regular review process, peer review for statistical content may be required for some manuscripts. This will be determined by the *Journal*'s Statistical Editors. Authors will be sent reviewer comments that are judged to be useful to them. All reviewers remain anonymous. Once the Editor has made a final decision on a paper, the authors of that paper will be informed.

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The original manuscript and three copies should be submitted to John C. Nemiah, M.D., Editor, *American Journal of Psychiatry,* 1400 K St., N.W., Washington, DC 20005. All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the *Journal* it is being submitted (i.e., Special Article, Regular Article, Brief Communication, or Clinical and Research Report); papers will only be reviewed after such a statement has been received from the author.

Authors will be notified of the receipt of their paper and the number assigned to it. **This number must be included in all further correspondence.** It is imperative that the corresponding author of submitted papers notify the *Journal* of changes of address. Because of escalating postage costs, no manuscripts submitted to the *Journal* will be returned to authors except upon special request. Authors must make this request in their original submission letter and include a self-addressed, postage-paid envelope.

Single Case Reports

Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients should include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

Annual Meeting Papers

Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

TYPES OF ARTICLES

Special Articles

These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

Regular Articles and Brief Communications

The only difference between these two types of papers is length. **Regular Articles** contain no more than 3,800 words, including an abstract of no more than 100 words, references, tables, and figures. **Brief Communications** contain no more than 2,500 words, including an abstract of no more than 100 words, references, tables, and figures. (A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words.) Articles that exceed 3,800 words will be returned unreviewed to the authors.

Clinical and Research Reports

A prompt publication policy (i.e., publication within 4 to 6 months after acceptance) is in effect for Clinical and Research Reports. Manuscripts may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including an abstract of no more than 40 words, text, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

Other Sections

Letters to the Editor. Brief letters (maximum of 500 words and 5 references; no tables or figures) will be considered if they include the notation "for publication." The number of words should appear in the upper right corner. Letters critical of an article published in the *Journal* will automatically be sent to the authors for reply. Because of space limitations not all letters can be printed. The *Journal* will notify authors about the disposition of their letters but does not return those that are not published. A letter must be signed by all of its authors. All letters will be edited; edited letters will not be sent to authors for approval. Letters must be typed **double-spaced** throughout on 8½×11 inch paper; three copies are required. Letters that do not meet these specifications will be returned for revision. Reprints are not available. **Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. Case reports submitted as Letters to the Editor will be peer reviewed.**

Book Forum. Books for review may be sent to the Book Forum Editor, Nancy C. Andreasen, M.D., Ph.D., University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242. Book reviews are usually solicited by the Book Forum Editor. Authors interested in reviewing a particular book should communicate directly with Dr. Andreasen. Reprints of reviews are not available.

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All parts of the manuscript, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8½×11 inch **nonerasable** bond paper. All four margins must be 1½ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

STYLE SPECIFICATIONS

Title Page

The number of words, tables, and figures in the paper and the telephone number of the corresponding author should be typed in the upper right-hand corner of the title page. At least three key words that describe the content of the paper should be typed in the lower right corner of the page.

Title. The title should be informative and as brief as possible. Two-part titles should be avoided.

By-line. Authors listed in the by-line should be limited to principal researchers and/or writers; collaborators may be acknowledged in a footnote. Authors' first names are preferred to initials. Degrees should be included after each author's name.

Previous presentation. If the paper has been presented at a meeting, please give the name of the meeting, the place, and the inclusive dates.

Location of work and address for reprints. Provide the department, institution, city, and state **where the work was done.** Include a full address for the author who is to receive reprint requests.

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Abstract

The abstract is a single paragraph no longer than 100 words for Special Articles, Regular Articles, and Brief Communications and no longer than 40 words for Clinical and Research Reports. Authors should use the active voice and the third person.

Text

Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. **All** significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3, 17$, $p<0.05$)." Reviewers will evaluate the appropriateness of the analyses.

Abbreviations. Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

References

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do **not** arrange the list alphabetically.

References should be restricted to closely pertinent material. **Accuracy of citation is the author's responsibility.** References should conform exactly to the original spelling, accents, punctuation, etc. Authors should be sure that all references listed have been cited in text.

Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not appear in the reference list. Such citations may be noted in text. It is the author's responsibility to obtain permission to refer to another individual's unpublished observations. Manuscripts that are actually "in press" may be cited as such in the reference list; the name of the journal or publisher and location must be included.

Type references in the style shown below, **double-spaced throughout.** List up to three authors; designate one or more authors past the third as "et al." Abbreviations of journal names should conform to the style used in *Index Medicus*; journals not indexed there should not be abbreviated.

1. Glick ID, Hargreaves WA, Drues J, et al: Short versus long hospitalization, a prospective controlled study, VII: two year follow-up results for nonschizophrenics. Arch Gen Psychiatry 1977; 34:314–320
2. McNamara JR (ed): Behavioral Approaches to Medicine. New York, Plenum Press, 1979
3. Janowsky DS, Judd LL, Huey L, et al: Effects of naloxone in normal, manic and schizophrenic patients: evidence for alleviation of manic symptoms, in Endorphins in Mental Health Research. Edited by Usdin E, Bunney WE Jr, Kline NS. New York, Oxford University Press, 1979

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Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

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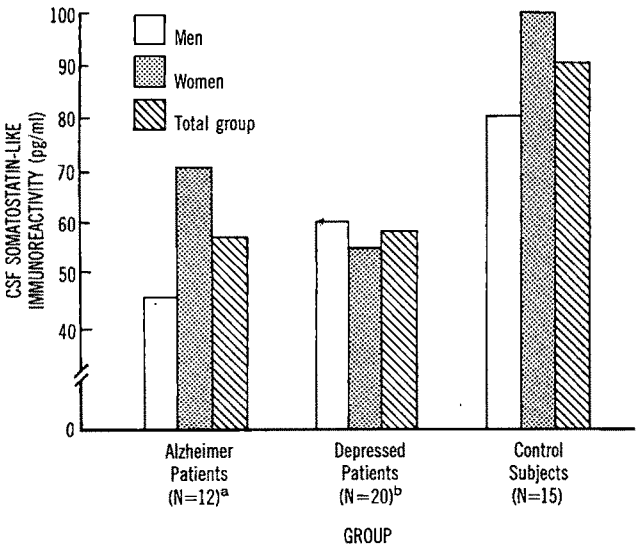
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Format. Figures are visual expressions of data trends or relationships. Figures that represent numerical data which could be expressed more succinctly or clearly in tabular form should be converted to tables. Line graphs should show change in continuous variables; comparisons of like values in different groups should be presented as bar graphs. Graphs containing stacked bars are unacceptable; the different segments of each bar should be presented side by side.

Lettering. Figure type should be sans serif and should be large enough to remain legible after the figure is reduced; most figures taking up the width of a vertical manuscript page are reduced to a width of 19.5 picas (3¼ inches), and those requiring a horizontal manuscript page are usually re-

FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



[a]Significant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).
[b]Significant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

duced to 40.5 picas (6¾ inches). When space on the horizontal axis is insufficient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

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1. Do not use solid black shading; rather, include outlined white among shadings.
2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.
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4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.
5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.
6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.
7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).
8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.
9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

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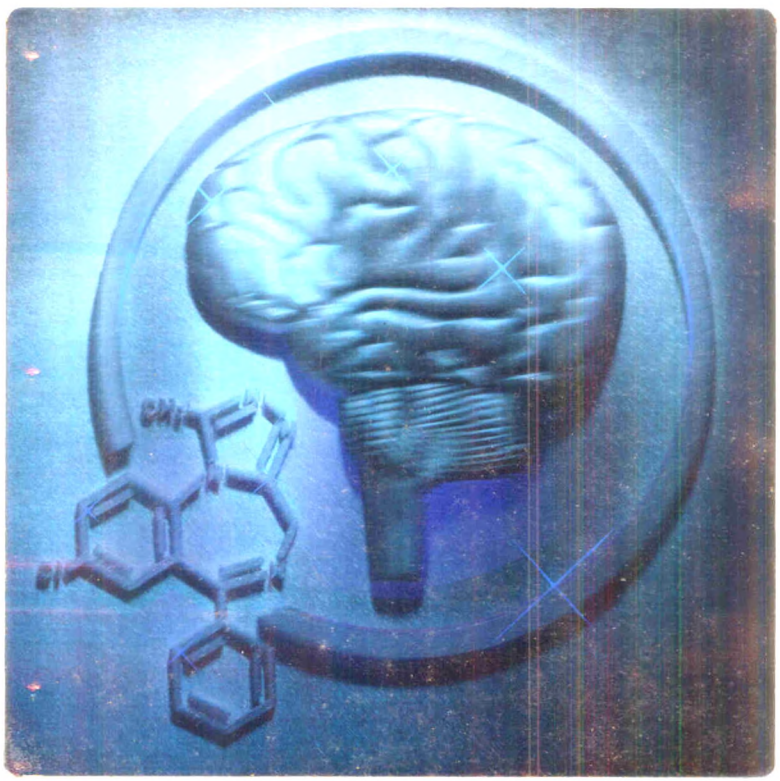
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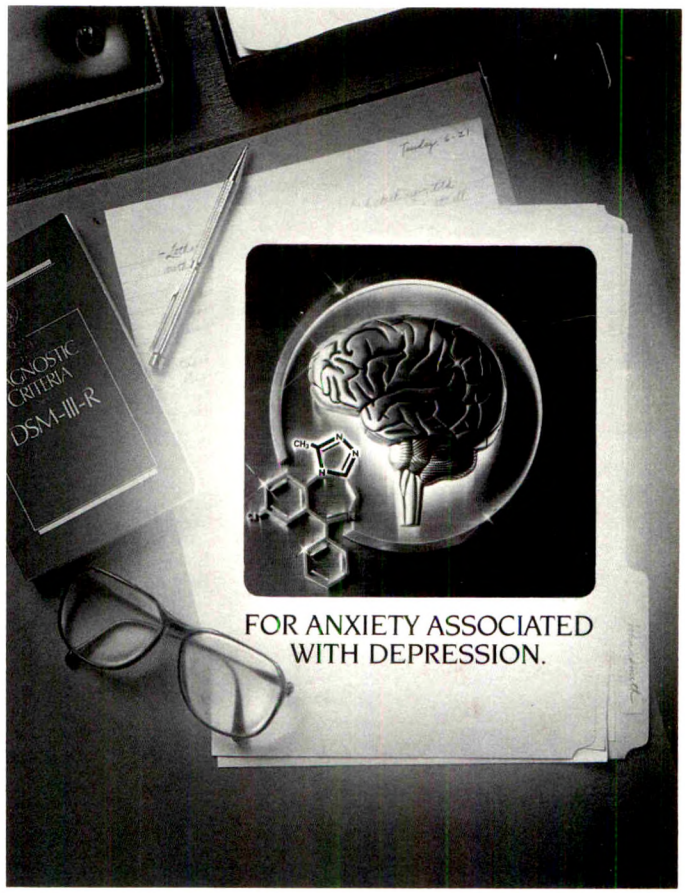
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INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration).

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration). Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings).

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

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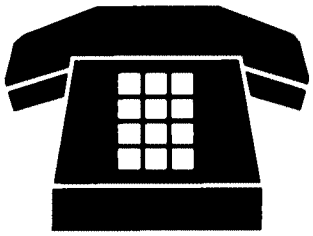
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Books Received

Unifying Individual and Family Therapies, by David M. Allen. San Francisco, Jossey-Bass, 1988, 360 pp., $27.95.

Worried Sick: Our Troubled Quest for Wellness, by Arthur J. Barsky, M.D. Boston, Little, Brown and Co., 1988, 255 pp., $17.95.

Mutative Metaphors in Psychotherapy: The Aeolian Mode, by Murray Cox and Alice Theilgaard. New York, Tavistock Publications (Routledge, distributor), 1987, 276 pp., $49.50; $18.95 (paper).

Concise Guide to Clinical Psychiatry, by Steven L. Dubovsky, M.D. Washington, D.C., American Psychiatric Press, 1988, 192 pp., $16.95 (paper).

Chronic Pain, edited by Randal D. France, M.D., and K. Ranga Rama Krishnan, M.D. Washington, D.C., American Psychiatric Press, 1988, 546 pp., $32.00.

Industrial Hygiene Management, edited by Jack T. Garrett, Lewis J. Cralley, and Lester V. Cralley. New York, John Wiley & Sons, 1988, 369 pp., $65.00.

Review of General Psychiatry, 2nd ed.: A Lange Medical Book, edited by Howard H. Goldman, M.D., M.P.H., Ph.D. Norwalk, Conn., Appleton & Lange, 1988, 671 pp., $25.00 (paper).

Anxiety and Its Treatment: Help Is Available, by John H. Greist, M.D., James W. Jefferson, M.D., and Isaac M. Marks, M.D. Washington, D.C., American Psychiatric Press, 1986, 189 pp., $15.95.

Concise Guide to Somatic Therapies in Psychiatry, by Laurence B. Guttmacher, M.D. Washington, D.C., American Psychiatric Press, 1988, 151 pp., $16.95 (paper).

Spiders and Flies: Help for Parents of Sexually Abused Children, by Donald Hillman and Janice Solek-Tefft. Lexington, Mass., Lexington Books (D.C. Heath and Co.), 1988, 196 pp., $24.95.

Consent and the Incompetent Patient: Ethics, Law, and Medicine: Proceedings of a Meeting Held at The Royal Society of Medicine, 9 December 1986, edited by Steven R. Hirsch and John Harris. London, Gaskell (Washington, D.C., American Psychiatric Press, distributor), 1988, 96 pp., £7.50 (paper).

Why We Sleep: The Functions of Sleep in Humans and Other Mammals, by James Horne. New York, Oxford University Press, 1988, 314 pp., $49.95.

Psychosis and Depression in the Elderly: Psychiatric Clinics of North America, vol. 11, number 1, March 1988, edited by Dilip V. Jeste, M.D., and Sidney Zisook, M.D. Philadelphia, W.B. Saunders Co. (Harcourt Brace Jovanovich), 1988, 277 pp., no price listed.

A Primer of Drug Action, 5th ed., by Robert M. Julien, M.D. New York, W.H. Freeman and Co., 1988, 354 pp., $24.95; $14.95 (paper).

The Art of Intervention in Dynamic Psychotherapy, by Bert L. Kaplan, Ed.D. Northvale, N.J., Jason Aronson, 1988, 257 pp., $25.00.

Westphal's "Die Agoraphobie" With Commentary: The Beginnings of Agoraphobia, by Terry J. Knapp and Michael T. Schumacher. Lanham, Md., University Press of America, 1988, 92 pp., $18.75; $9.25 (paper).

Unbalanced Accounts: How Women Can Overcome Their Fear of Money, by Annette Lieberman and Vicki Lindner. New York, Penguin Books, 1987, 281 pp., $7.95 (paper).

Dreams and Psychosynthesis, by Alton Löker. Istanbul, Altan Löker, 1987, 236 pp., $7.00 (paper).

The Children at Santa Clara, by Elizabeth Marek. New York, Penguin Books, 1988, 177 pp., $6.95 (paper).

Hermeneutics and Psychological Theory: Interpretive Perspectives on Personality, Psychotherapy, and Psychopathology, edited by Stanley B. Messer, Louis A. Sass, and Robert L. Woolfolk. New Brunswick, N.J., Rutgers University Press, 1988, 408 pp., $45.00; $20.00 (paper).

Gay, Straight, and In-Between: The Sexology of Erotic Orientation, by John Money. New York, Oxford University Press, 1988, 247 pp., $29.95.

The Psychobiology of Bulimia Nervosa, edited by K.M. Pirke, W. Vandereycken, and D. Ploog. New York, Springer-Verlag, 1988, 181 pp., $44.00 (paper).

New Concepts in Psychoanalytic Psychotherapy, edited by John Munder Ross, Ph.D., and Wayne A. Myers, M.D. Washington, D.C., American Psychiatric Press, 1988, 278 pp., $32.00.

Pragmatics of Psychotherapy: A Survey of Theories and Practices, by William Schofield. New Brunswick, N.J., Transaction Books, 1988, 200 pp., $32.95.

How To Survive Your Aging Parents So You and They Can Enjoy Life, by Bernard H. Shulman, M.D., and Raeann Berman. Chicago, Ill., Surrey Books, 1988, 187 pp., $10.95 (paper).

Selected Models of Anxiety, Depression and Psychosis, edited by P. Simon, P. Soubrié, and D. Wildlocher. Basel, Karger, 1988, 194 pp., $119.50.

You're Our Child: The Adoption Experience, by Jerome Smith, Ph.D., and Franklin I. Miroff. Lanham, Md., Madison Books, 1987, 221 pp., $9.95 (paper).

Psychiatric House Calls, edited by John A. Talbott, M.D., and Alan Z.A. Manevitz, M.D. Washington, D.C., American Psychiatric Press, 1988, 353 pp., $38.50.

Treating Obsessive-Compulsive Disorder, by Samuel M. Turner and Deborah C. Biedel. Oxford, Pergamon Press, 1988, 117 pp., $22.50; $12.95 (paper).

Enfermedad Mental y Entorno Urbano: Metodología e Investigación, by J.L. Martí Tusquets and M.J. Murcia Grau. Barcelona, Anthropos Editorial del Hombre, 1988, 292 pp., no price listed (paper).

Concise Guide to Consultation Psychiatry, by Michael G. Wise, M.D., and James R. Rundell, M.D. Washington, D.C., American Psychiatric Press, 1988, 175 pp., $15.95 (paper).

The Technique of Psychotherapy, 4th ed., parts 1 and 2, by Lewis R. Wolberg, M.D. Orlando, Fla., Grune & Stratton (Harcourt Brace Jovanovich) (Philadelphia, W.B. Saunders, distributor), 1988, 1,640 pp., $139.50.

Using Reality Therapy, by Robert E. Wubbolding. New York, Perennial Library (Harper & Row), 1988, 176 pp., $15.95; $7.95 (paper).

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THE BRITISH JOURNAL OF PSYCHIATRY

JUNE 1988 VOLUME 152

Annotation

Acetylcholine and Alzheimer's disease. *E. Perry* 737

Review Article

Molecular genetics and human disease: complications for modern psychiatric research and practice. *M. Baron and J.D. Rainer* 741

Papers

The Camberwell Collaborative Depression Study:
I. Depressed probands: adversity and the form of depression. *P.E. Bebbington, T. Brugha, B. MacCarthy, J. Potter, E. Sturt, T. Wykes, R. Katz and P. McGuffin* 754

II. Investigation of family members. *P. McGuffin, R. Katz, J. Aldrich and P. Bebbington* 766

III. Depression and adversity in the relatives of depressed probands. *P. McGuffin, R. Katz and P. Bebbington* 775

The practice of community psychiatric nursing and mental health social work in Salford: some implications for community care. *K. Wooff, D.P. Goldberg and T. Fryers* 783

Decline in the diagnosis of schizophrenia among first contacts with psychiatric services in north-east Scotland, 1969–1984. *J.M. Eagles, D. Hunter and C. McCance* 793

Non-psychotic psychiatric disorder after childbirth: a prospective study of prevalence, incidence, course and nature. *P.J. Cooper, E.A. Campbell, A. Day, H. Kennerley and A. Bond* 799

Emotional disturbances in endocrine patients: validity of the scaled version of the general health questionnaire (GHQ-28). *A. Lobo, M.J. Pérez-Echeverría, A. Jiménez-Aznárez and M.A. Sancho* 807

A follow-up study on alcoholics with and without co-existing affective disorder. *K. O'Sullivan, C. Rynne, J. Miller, S. O'Sullivan, V. Fitzpatrick, M. Hux, J. Cooney and A. Clare* 813

Influence of climate on the prevalence of mania. *P.A. Carney, C.T. Fitzgerald and C.E. Monaghan* 820

Supportive analytical psychotherapy: an account of two cases. *J. Holmes* 824

The accident and emergency department management of deliberate self-poisoning. *D.W. Owens and S.J. Jones* 830

School refusal: a 15–20-year follow-up study of 35 Swedish urban children. *N. Flakierska, M. Lindström and C. Gillberg* 834

Brief reports

True hallucinations as a culturally sanctioned experience. *C. Andrade, S. Srinath and A. Andrade* 838

Two cases of hypomania in AIDS. *U. Schmidt and D. Miller* 839

Pica as a cause of death in three mentally handicapped men. *I.J. McLoughlin* 842

Shop-lifting as a symptom of stress in families of mentally handicapped persons: a case report. *M. Roy* 845

Down's syndrome and eating disorders: a case study. *G.M. Holt, N. Bouras and J.P. Watson* 847

The mentally handicapped criminal offender: a 10-year study of two hospitals. *A. Kearns and A. O'Connor* 848

Monosymptomatic hypochondriasis treated with a tricyclic antidepressant. *N. Fernando* 851

Severe memory impairment with acute overdose lithium toxicity: a case report. *S. Saxena and P. Mallikarjuna* 853

Correspondence 855

A hundred years ago. *Researched by Henry Rollin* 868

Reading about . . . *Mental handicap: update. B. Kirman* 869

Reprinted for the information of the readers of the American Journal of Psychiatry

THE BRITISH JOURNAL OF PSYCHIATRY

JULY 1988 VOLUME 153

Annotation

Fatigue and fatigability. *H.G. Kennedy* 1

Review Article

Self-esteem: a psychiatrist's view. *P.J. Robson* 6

Lecture

Assessing the epidemiology of suicide and parasuicide. *R.D.T. Farmer* 16

Papers

The relationship between psychiatric research and public policy. *L. Eisenberg* 21

Further observations on the practice of community care in Salford: differences between community psychiatric nurses and mental health social workers. *K. Wooff and D.P. Goldberg* 30

Psychiatric morbidity and social problems in patients with insulin-dependent diabetes mellitus. *G. Wilkinson, D.Q. Borsey, P. Leslie, R.W. Newton, C. Lind and C.B. Ballinger* 38

Personality disorder: the patients psychiatrists dislike. *G. Lewis and L. Appleby* 44

The aetiology of aggression in temporal lobe epilepsy. *J.L. Herzberg and P.B.C. Fenwick* 50

Depression and the physical environment: a study of young married women on a London housing estate. *J. Birtchnell, N. Masters and M. Deahl* 56

Blunted response of growth hormone to clonidine and apomorphine in endogenous depression. *M. Ansseau, R. von Frenckell, J.L. Cerfontaine, P. Papart, G. Franck, M. Timsit-Berthier, V. Geenen and J.J. Legros* 65

Physical complications in anorexia nervosa: haematological and neuromuscular changes in 12 patients. *E. Shur, R. Alloway, R. Obrecht and G.F.M. Russell* 72

Hyperventilation in panic attacks: ambulant monitoring of transcutaneous carbon dioxide. *G. Hibbert and D. Pilsbury* 76

Child and family factors associated with referral to child psychiatrists. *M.E. Garralda and D. Bailey* 81

A matched-control follow-up and family study of 'puerperal psychoses'. *C. Platz and R.E. Kendall* 90

Comprehension and motivation in responses to a psychiatric screening instrument. *F. Kortmann and S. Ten Horn* 95

Brief reports

Hypothyroidism in Down's syndrome. *C. Mani* 102

Prospective electroconvulsive therapy in a delusional depressed patient with a frontal meningioma: a case report. *L.B. Greenberg, R. Mofson and M. Fink* 105

Spectrum concept of neuroleptic malignant syndrome. *Adityanjee, S. Singh, G. Singh and S. Ong* 107

Writer's cramp: a controlled trial of habit reversal treatment. *A. Wieck, R. Harrington, I. Marks and C. Marsden* 111

Sex differences in the seasonal distribution of suicides. *D. Lester and M.L. Frank* 115

Capgras syndrome heralding the development of dementia. *B. Lipkin* 117

Correspondence 119

A hundred years ago. *Researched by Henry Rollin* 131

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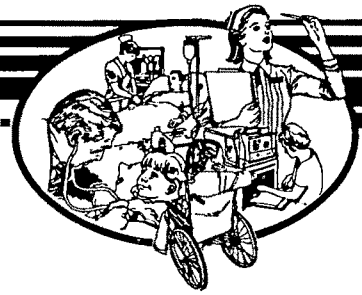
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Candidates must possess Canadian or equivalent qualifications. While these positions are open to all qualified applicants, in compliance with Canadian Immigration regulations, preference will be given to Canadian Citizens or landed immigrants.

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Interested psychiatrists are invited to submit a recent curriculum vitae and letter of application to:

J. Arboleda-Florez, M.D., Director
Department of Psychiatry
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